Janssen Research & Development, LLC

Advisory Committee Briefing Document

LEVAQUIN® **for Pneumonic Plague**

JNJ-17080271; R307218; RWJ-25213 (levofloxacin)

LEVAQUIN ® (levofloxacin) Tablets - NDA 20-634/S-061
LEVAQUIN ® (levofloxacin) Injection - NDA 20-635/S-067
LEVAQUIN ® (levofloxacin) Oral Solution - NDA 21-721/ S-028

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Issue/Report Date: 27 February 2012
Document No.: EDMS-ERI-35299601: 1.0

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ATTACHMENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADME	Absorption, distribution, metabolism, excretion
AGM	African Green Monkey
AUC	Area under the plasma/serum concentration-time curve
BID	Twice daily
BBRC	Battelle Biomedical Research Center
BSGT	buffered saline with 0.01% gelatin and 9.7% trehalose
C	Celsius
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control
C.E.	Common Era
CFR	Code of Federal Regulations
CFU	colony forming units
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum concentration
DOD	Department of Defense
DNA	Deoxyribonucleic acid
DSPTP	Division of Special Pathogens and Transplant Products
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
h	hour
HIB	Heart Infusion Broth
i.p.	intraperitoneal
IV	Intravenous
Janssen	Janssen Research & Development, LLC
kg	kilogram
LBERI	Lovelace Biomedical and Environmental Research Institute
LD_{50}	50% of the lethal dose
LRRI	Lovelace Respiratory Research Institute
MDRSP	Methicillin-drug-resistant *Streptococcus pneumoniae*
MEF	Middle ear fluid
mg	milligram
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum inhibitory concentration at which 50% of isolates are inhibited
MIC_{90}	Minimum inhibitory concentration at which 90% of isolates are inhibited
min	minute
mL	milliliter
MS	Musculoskeletal
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PK	pharmacokinetic
p.o.	*Per os*; by mouth
PSUR	Periodic Safety Update Report
QD	Once daily

sNDA	Supplemental New Drug Application
$t_{1/2}$	half life
TSA	tryptic soy agar
T_{max}	Time to maximum concentration
µg	microgram
U.S.	United States
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
USPI	United States package insert
Y. pestis	*Yersinia pestis*

1. EXECUTIVE SUMMARY

LEVAQUIN® (levofloxacin) is an FDA-approved, synthetic broad-spectrum antibacterial agent being submitted for approval of a new indication based on research by the National Institute of Allergy and Infectious Diseases (NIAID) for the treatment of inhalational plague in case of bioterrorism attacks. The proposed recommended dosage regimen for adults and pediatric patients weighing ≥50 kilogram (kg) and ≥6 months of age is 500 milligram (mg) given once daily for 14 days either orally or intravenously (IV), and for pediatric patients weighing <50 kg and ≥6 months of age, the recommended dosage regimen is 8 mg/kg twice a day (not to exceed 250 mg/dose) for 14 days.

LEVAQUIN exhibits in vitro activity against a wide range of Gram-negative and Gram-positive microorganisms and is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. LEVAQUIN was first approved in the United States (U.S.) by FDA on December 20, 1996 and is available in 3 formulations: oral tablet (New Drug Application [NDA] 20-634), injectable (NDA 20-635), and oral solution (NDA 21-721). With the U.S. patent expiry in June, 2011, generic equivalents have become available.

The estimated exposure to LEVAQUIN in the U.S. is approximately 300 million treatment courses as of 31 March 2011, and it has a well-defined and predictable safety profile at dosage regimens in adults of 500 mg given once daily for up to 28 days and 750 mg given once daily for up to 14 days. As the proposed dosing regimen for pneumonic plague (post-exposure) is the same or lower dose and the same or shorter duration than the approved dosing regimens in adults for nosocomial pneumonia, community-acquired pneumonia, acute bacterial sinusitis, complicated skin and skin structure infections, chronic bacterial prostatitis and inhalational anthrax (post-exposure) a similar safety profile would be expected. In the same way, the proposed pediatric dosage recommendation for plague (post-exposure) is the same dose, but for shorter duration, than the currently approved recommended pediatric dose for inhalational anthrax (post-exposure).

Yersinia pestis (Y. pestis), the causative agent of plague, is one of a limited number of agents identified by the Working Group for Civilian Biodefense that, if used as weapons, could cause disease and death in sufficient numbers to cripple a city or region.[30] *Y. pestis* has several characteristics that make it a significant concern for use as a biological weapon: it can be found in many regions of the world, can be mass-produced, and can be disseminated through direct aerosolization. Importantly, unlike other potential biological weapons, such as anthrax, it can be spread through person-to-person contact and therefore has high potential for secondary spread of cases during an epidemic. In addition, the pneumonic form of the disease has rapid onset of signs and symptoms and has a very high fatality rate. All of these characteristics are key factors underlying its classification as a Category A Bioterrorism Agent in the U.S.[41]

Currently, there are no FDA-approved antibacterials specifically indicated for the treatment of pneumonic plague (resulting from the direct inhalation of *Y. pestis*) for adult or pediatric use. In addition, there is presently no FDA-approved vaccine for plague caused by *Y. pestis*. Based on

fulfilling the core justification for priority review, Janssen Research & Development, LLC (hereafter referred to as Janssen) requested a priority review of the Supplemental New Drug Applications (sNDAs) for the pneumonic plague indication. FDA granted priority review status on 27 December 2011.

Because of the obvious ethical concerns and infeasibility, evaluation in humans of the efficacy of LEVAQUIN in the treatment of pneumonic plague is not appropriate and must rely on studies using animal models. Thus, the development of this indication relied on adherence to the Animal Rule. In accordance with 21 Code of Federal Regulations (CFR) 314.610, (i.e., the Animal Rule), FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

- There is a reasonably well-understood pathophysiological mechanism of the toxicity of the (chemical, biological, radiological, or nuclear) substance and its prevention or substantial reduction by the product.
- The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.
- The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.
- The data on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans (21 CFR 314.610(a)(1)-(4)).

The data from levofloxacin nonclinical studies provide evidence of the drug's effectiveness as a potential life-saving therapy for the treatment of pneumonic plague following inhalation of *Y. pestis*.

As is the case for other agents from the fluoroquinolone class (e.g., ofloxacin, ciprofloxacin and moxifloxacin), several studies have shown that levofloxacin exhibits potent in vitro activity against *Y. pestis*.[20] Levofloxacin and ofloxacin (a racemic mixture which consists of 50% levofloxacin) have been reported to be efficacious in both rodent[27,48,52] and primate[33,49] models of *Y. pestis* infection. Further, there have not been any reports of clinical *Y. pestis* isolates resistant to fluoroquinolones. This is in contrast to reports that have documented resistance to antibacterials recommended for therapy and prophylaxis of *Y. pestis* infections (chloramphenicol, streptomycin, sulfonamides, and tetracycline) as well as others including ampicillin, kanamycin, spectinomycin and minocycline.[23, 25]

The African Green Monkey (AGM) pneumonic plague model is a well-characterized animal model for predicting the response in humans infected with *Y. pestis*. Studies conducted to characterize the natural history disease progression of pneumonic plague following aerosol exposure of AGMs to *Y. pestis* confirmed that the disease in AGMs shares many features with human clinical disease (Studies F03-09G, FY06-126, 617-G607610, and 875-G607610) (see

NIAID summary of natural history studies in Attachment 1). The clinical presentations in AGMs are very similar to those in humans, including fever in 100% of cases (typically 3 days post-exposure in AGMs), the presence of *Y. pestis* in body fluids, elevated heart rate, elevated respiratory rate late in the disease, pulmonary infiltrates (most frequently bilateral) on chest radiographs, and similar lung pathologies. The similarities observed between humans and AGMs in the clinical presentations of pneumonic plague indicate that the AGM pneumonic plague model is a satisfactory model of human pneumonic plague (see Attachment 1).

In the pivotal efficacy study in the AGM model of pneumonic plague (Study FY07-070), levofloxacin 8 mg/kg administered intravenously for 10 days followed by a single 2 mg/kg dose 12 hours later (i.e., a dosing regimen designed to approximate human exposure) resulted in a 94% survival rate (16 of 17 animals) compared to a 0% survival rate in untreated control animals (a statistically significant difference, $p \leq 0.001$ by Fisher's Exact Test). This dosing regimen in AGMs achieved 53% of the human maximum concentration (C_{max}) and 25% of the area under the plasma/serum concentration-time curve $(AUC)_{0-24}$ in humans. Fever in the treated survivors typically resolved in 3 to 4 days while bacteremia resolved before the next daily blood draw. The 1 levofloxacin-treated animal that died (Y160) was euthanized on Day 9 due to vomiting and inability to retain food. This death did not appear to be related to *Y. pestis* infection, as evidenced by daily blood cultures (Days 2 to 7) and tissues collected at necropsy that were all negative for *Y. pestis*; the exact cause of death remains unexplained.

The results of the pivotal efficacy study in AGMs (Study FY07-070), along with the studies of the natural history of plague in AGMs, the in vitro microbiology data, data in rodent models of plague and the literature collectively satisfy each of the 4 conditions outlined above under the Animal Rule. Thus, the Sponsor proposes that the data from Study FY07-070 and supporting information from the literature on the efficacy of levofloxacin in vitro and in rodent models of plague infection provide the substantial evidence of effectiveness outlined in 21 CFR 314.610.

The Animal Rule requires that the safety of the product be demonstrated in humans and permits data from the product's use in other indications to be used as a critical component of the benefit/risk analysis of the product. The estimated exposure to LEVAQUIN in the U.S. is approximately 300 million treatment courses as of 31 March 2011, and it has a well-characterized and predictable safety profile at dosage regimens in adults of 500 mg given once daily for up to 28 days and 750 mg given once daily for up to 14 days. The proposed dosing recommendations for pneumonic plague (post-exposure) are for the same or lower doses and the same or shorter duration than the approved dosage regimens in adults for nosocomial pneumonia, community-acquired pneumonia, acute bacterial sinusitis, complicated skin and skin structure infections, chronic bacterial prostatitis and inhalational anthrax (post-exposure). The proposed pediatric dosage recommendation for plague (post-exposure) is also for the same dose but for shorter duration than the recommended pediatric dose for inhalational anthrax (post-exposure). Given the relatively short treatment period for pneumonic plague, no new safety issues are likely. The previous findings of clinical safety for LEVAQUIN for currently approved indications and as stated in the United States Package Insert (USPI) (see Attachment 2) meet the requirements for clinical safety assessment as defined in the Animal Rule.

Levofloxacin is well-suited to treat the pneumonic form of plague, based on its excellent tissue penetration in the lung and significant clinical experience in more than 2,000 patients with community-acquired pneumonia (CAP) in prospective clinical trials. Levofloxacin exhibits extensive distribution into lung tissue and high steady-state concentrations in intrapulmonary compartments including the epithelial lining fluid for up to 24 hours with 500 mg once-daily dosing. [24]

In a mass casualty setting, administration of parenteral antibiotic therapies would be impractical, if not impossible, due to logistics, shortages of supplies and trained personnel necessary to administer them. Therefore, an approved oral antibiotic therapy would be highly preferred in a scenario in which large portions of the population are exposed to *Y. pestis*. In addition to being available in both oral and parenteral formulations, levofloxacin also offers other advantages for use in a mass casualty setting, such as availability of adequate drug supplies, once-daily dosing, high oral bioavailability, no food interactions, low potential for drug-drug interactions, and proven safety profile.

Following its approval for anthrax (post-exposure), supplies of both oral and parenteral formulations of LEVAQUIN have been stockpiled by the Centers for Disease Control (CDC) and the Department of Defense (DOD). LEVAQUIN has a shelf-life of up to 2 years and products are available in sizes small enough to facilitate storage of large quantities which can also be readily shipped in the event of an emergency. The existing stockpiles of LEVAQUIN as well as generic formulations of levofloxacin would be able to meet demand in the event of a bioterrorism attack were LEVAQUIN also approved for pneumonic plague (post-exposure).

For all the reasons cited above, LEVAQUIN could potentially save many lives of individuals exposed to *Y. pestis* in a bioterrorist attack. Given the well-defined and predictable safety profile of LEVAQUIN and its suitability for use in a mass casualty setting, it is clear that any potential risk of LEVAQUIN administration is outweighed by the treatment benefits of the use of LEVAQUIN for the indication pneumonic plague (post-exposure).

The availability of an FDA-approved product with the proposed indication for pneumonic plague following exposure to *Y. pestis* would be expected to yield meaningful public health benefits in the event of a bioterrorism attack involving dissemination of *Y. pestis*. Janssen is appreciative of the Committee's review of LEVAQUIN for this purpose and looks forward to your input.

2. INTRODUCTION

2.1. Overview of LEVAQUIN

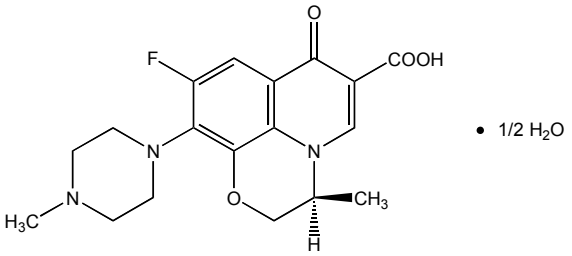
2.1.1. Proposed Indication and Dosage Recommendation

The proposed indication in the sNDAs for LEVAQUIN (levofloxacin) is pneumonic plague following exposure to *Y. pestis*. The proposed recommended dosage regimen for adults and pediatric patients weighing ≥50 kg and ≥6 months of age is 500 mg given once daily for 14 days either orally or IV, and for pediatric patients weighing <50 kg and ≥6 months of age, the recommended dosage regimen is 8 mg/kg twice a day (not to exceed 250 mg/dose) for 14 days.

2.1.2. Product Description

LEVAQUIN (levofloxacin) is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

Figure 1: Chemical Structure of Levofloxacin



LEVAQUIN exhibits in vitro activity against a wide range of Gram-negative and Gram-positive microorganisms and is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials is inhibition of the bacterial Type II deoxyribonucleic acid (DNA) Topoisomerase enzymes, Topoisomerase IV and DNA gyrase, that play essential roles in DNA replication, transcription, repair and recombination. *Y. pestis* has been evaluated in several studies comprising 600 *Y. pestis* isolates with levofloxacin MIC_{50} (the minimum inhibitory concentration at which 50% of isolates are inhibited) values of ≤0.03 microgram (µg)/milliliter (mL) and MIC_{90} (the minimum inhibitory concentration at which 90% of isolates are inhibited) values of 0.06 µg/mL (Table 1).

2.1.3. Current LEVAQUIN Indications

LEVAQUIN was first approved in the U.S. by FDA on December 20, 1996 and is available in 3 formulations: oral tablet (NDA 20-634), injectable (NDA 20-635), and oral solution (NDA 21-721). The patent on LEVAQUIN expired in June, 2011. The current indications for LEVAQUIN are as follows:

(i) Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae*, or *Streptococcus pneumoniae* with adjunctive therapy recommended as clinically indicated.

(ii) Community-acquired pneumonia (7–14 day treatment regimen) due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant *Streptococcus pneumoniae* [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis*, *Chlamydophila pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae.*

(iii) Community-acquired pneumonia (5-day treatment regimen) due to *Streptococcus pneumoniae* (excluding multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae,* or *Chlamydophila pneumoniae*.

(iv) Acute bacterial sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis*.

(v) Acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Moraxella catarrhalis*.

(vi) Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes*, or *Proteus mirabilis*.

(vii) Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible *Staphylococcus aureus*, or *Streptococcus pyogenes*.

(viii) Chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis,* or methicillin-susceptible *Staphylococcus epidermidis.*

(ix) Complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis*.

(x) Complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, or *Pseudomonas aeruginosa.*

(xi) Acute pyelonephritis caused by *Escherichia coli*, including cases with concurrent bacteremia,

(xii) Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae,* or *Staphylococcus saprophyticus.*

(xiii) Inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

Based on studies in Rhesus monkeys, LEVAQUIN was approved by FDA in November 2004 (adults) and May 2008 (pediatric patients) for the treatment of inhalational anthrax (post-exposure). The recommended dose regimen in adults and children weighing ≥50 kg and ≥6 months of age is 500 mg given once daily for 60 days. For children weighing <50 kg and ≥6 months of age, the recommended dosage regimen is 8 mg/kg twice a day (not to exceed 250 mg/dose) for 60 days.

The current approved USPI for LEVAQUIN can be found in Attachment 2.

2.2. Overview of Pneumonic Plague

Y. pestis, the causative agent of plague, is one of a limited number of agents identified by the Working Group for Civilian Biodefense that, if used as weapons, could cause disease and death in sufficient numbers to cripple a city or region.[30] *Y. pestis* has several characteristics that make it a significant concern for use as a biological weapon: it can be found in many regions of the world, can be mass-produced, can be disseminated through direct aerosolization, can be spread through person-to-person contact and therefore has high potential for secondary spread of cases during an epidemic, has rapid onset of lethal symptoms and has a very high fatality rate in the pneumonic form of the disease. All of these characteristics are key factors underlying its classification as a Category A Bioterrorism Agent in the U.S.[41]

Plague is an infectious disease that affects animals and humans and is caused by the non-motile Gram-negative bacillus *Y. pestis*. Natural reservoirs for *Y. pestis* exist predominately in wild rodent populations, especially ground squirrels, chipmunks and prairie dogs and their associated flea species.[47,30] A variety of other wild rodents, including rats and mice, and also cats and dogs can become infected with plague and the disease is occasionally transmitted to people who are bitten by infected animals or by fleas that have fed on infected animals. As a prelude to human epidemics, rats frequently die in large numbers in endemic areas precipitating the movement of the flea population from its natural reservoir to humans.

Y. pestis infections in humans are associated with 3 clinical manifestations: bubonic plague, septicemic plague, and pneumonic plague. Pneumonic plague is highly contagious and can spread from person to person through inhalation of aerosolized bacteria in respiratory droplets during close contact with infected persons (or animals).[17] Secondary pneumonic plague develops in a minority of patients with bubonic or primary septicemic plague (approximately 12% of total cases in the U.S. over the last 50 years[47]) through hematogenous spread of plague bacilli to the lungs. Pneumonic plague is associated with many of the same symptoms as the bubonic and septicemic forms of the disease but with additional symptoms of dyspnea, chest pain, cough and hemoptysis. Symptoms usually progress for 2 to 4 days, and without prompt medical intervention, can be accompanied by sepsis and may progress rapidly to respiratory failure and shock, with death typically occurring within 2 to 6 days after symptoms begin.

The first recorded human plague pandemic began in Egypt in 541 Common Era (C.E.) and spread rapidly with high mortality rates in North Africa, Europe and central and southern Asia.[47] The second plague pandemic, also known as the 'Black Death' or 'Great Pestilence', began in 1346 and lasted 130 years and is estimated to have killed up to 30 million people in Europe – one third of the European population.[54] The last global pandemic began in China in 1855 and is estimated to have killed more than 12 million people in India and China alone.[47] While advances in living conditions, public health and the availability of effective antibiotic therapy make future global pandemics improbable, outbreaks of plague continue to occur throughout the world.[47,54,30,9,39]

In the absence of antibiotic treatment, the mortality rate from septicemic or pneumonic plague is essentially 100%.[17] All forms of plague are associated with high rates of mortality; significantly elevated rates of mortality are observed in patients in whom antibiotic treatment is delayed more than 24 hours after the onset of symptoms.[30] In the U.S., 390 cases of plague were reported from 1947 to 1996, 84% of which were bubonic, 13% septicemic and 2% pneumonic with concomitant fatality rates of 14%, 22% and 57%, respectively.[8]

In the Middle Ages, plague was used as a biological weapon when armies catapulted dead plague victims into cities under siege to spread the disease.[46] Japan also employed plague as a biological weapon against the Chinese during World War II by dropping plague-infected fleas over populated areas which caused outbreaks of the disease.[39,46] In the years following World War II, biological weapons programs in the U.S. and the Soviet Union developed techniques for aerosolizing *Y. pestis*.[30] A 1970 World Health Organization report estimated that an aerosol release of 50 kg of dried powder containing 6×10^{15} *Y. pestis* bacteria over a city of 5 million people in an economically developed country (such as the U.S.) would produce 150,000 incapacitating illnesses, and as many as 36,000 deaths.[26] These estimates did not take into consideration secondary cases that would occur through subsequent person-to-person contact.

2.3. Unmet Medical and Public Health Need

Currently, there are no FDA-approved drugs for the treatment of pneumonic plague caused by *Y. pestis*, largely driven by the difficulty in clinical evaluation and the low risk of natural occurrence of such infections. Nonetheless, based on the potential for the use of this pathogen in bioterrorism, availability of safe and effective options are of critical importance to the safety and security of the public. To date, treatment guidelines have relied on empiric clinical observations combined with data from in vitro susceptibility studies and data from efficacy studies of antibacterials in rodent animal models of plague disease. The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals following the use of plague as a biological weapon against a civilian population.[30] The current recommendations include parenteral forms of the antimicrobials streptomycin or gentamicin in a contained casualty setting. In a mass casualty setting, the current recommendation is for oral therapy, preferably with doxycycline, or tetracycline or ciprofloxacin. However, none of these drugs is approved in the U.S. specifically for pneumonic plague (post-exposure) and may be of limited usefulness in a mass casualty

setting due to lack of availability in the U.S., lack of availability in an oral formulation, and restrictions on use in children, pregnant women, and special populations.

The fluoroquinolone family of antibacterials typically show potent in vitro activity against *Yersinia* species, including human clinical isolates of *Y. pestis*. Several agents have been shown to be efficacious in systemic and pneumonic animal models of plague disease.[5,7] Levofloxacin has been shown to have in vitro activity against *Y. pestis* clinical isolates with low MIC_{90} values (<0.03 to 0.06 µg/mL) being reported in both NIAID-sponsored studies (Study HPA-YpLMIC-2008, Study RIID-YpLMIC-2005) and published literature.[20,52,36] Levofloxacin was superior to streptomycin in an in vitro pharmacodynamic hollow-fiber model of *Y. pestis* infection.[37] In animal studies of plague disease, levofloxacin and/or ofloxacin (a racemic mixture which consists of 50% levofloxacin) have been reported to be efficacious both in rodent and primate, including both baboon and AGM models of *Y. pestis* infection, demonstrated in NIAID-sponsored studies (Study RIID-YpEf-2006, Study UTMB-YpEff-1-8, Study FY7-070) and in the published literature.[7,51,52,5,27,48,53,49,33]

2.4. Development of LEVAQUIN for Plague

2.4.1. Collaboration with NIAID

In 2003, Janssen was asked by NIAID to consider the development of LEVAQUIN for the treatment of inhalational plague in the event of bioterrorism attacks. To assist NIAID in the planning of their development program in pneumonic plague, Janssen presented data from the previous experience in conducting a successful anthrax efficacy study in Rhesus monkeys using a unique dosing regimen that established an effective dose in humans based on pharmacokinetic data.[32] (See Section 2.1.3 for the approved anthrax indication.)

LEVAQUIN (levofloxacin) was identified as a potential option for treatment of *Y. pestis* in the event of a biological attack by a National Institutes of Health (NIH) – FDA interagency working group established to identify therapeutic options for prophylaxis and treatment of various diseases caused by bioterrorism. Levofloxacin was selected for pneumonic plague efficacy testing because it possesses the following desirable characteristics for use in this eventuality:

- Levofloxacin and other members of the fluoroquinolone class of antibacterials show potent in vitro and small animal activity against *Yersinia* species.
- Levofloxacin penetrates well into the respiratory tract and achieves high concentrations in the relevant pulmonary compartments.[34,2,57]
- LEVAQUIN (levofloxacin) was approved by the FDA in November 2004 (adults) and May 2008 (pediatric patients) for the treatment of inhalational anthrax (post-exposure), a disease with a similar route of acquisition as plague, to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis* (Attachment 2).
- LEVAQUIN has been approved in the U.S. since 1996 and the estimated exposure in the U.S. is approximately 300 million treatment courses as of 31 March 2011. Its safety profile has been well characterized at a dosage regimen in adults of 500 to 750 mg usually given once daily for up to 28 days.

- LEVAQUIN is available in both oral and parenteral (IV) formulations, which can be used interchangeably. The oral formulation is essentially 100% bioavailable. This is an important attribute for a mass casualty setting. Levofloxacin C_{max} was 6.4 ± 0.8 µg/mL and AUC 54.6 ± 11.1 µg/ hour (h)/mL following IV injection of 500 mg levofloxacin once daily in healthy volunteers.

In 2010 after completion of NIAID's program, Janssen agreed to NIAID's request to submit their data in support of a new indication for LEVAQUIN for pneumonic plague following exposure to *Y. pestis*.

2.4.2. Regulatory History

Once the agreement was made that Janssen would file data provided by NIAID to the LEVAQUIN NDAs, Janssen initiated discussions with the FDA. On December 1, 2010, a pre-NDA meeting was held between Janssen, NIAID, and FDA's Division of Special Pathogens and Transplant Products (DSPTP) to discuss the format and content of the sNDAs.

In a follow-up to the pre-NDA meeting, General Advice correspondence was issued on 7 February 2011, FDA confirmed review of this application to be done under the provisions of 21 CFR 314.610, Subpart I ("Animal Rule") – Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible. The Agency agreed the Animal Rule is an appropriate regulatory pathway for developing levofloxacin for the treatment of pneumonic plague. The Agency agreed that the data from the single Good Laboratory Practices (GLP) animal efficacy study conducted in AGMs combined with information from the literature on rodents, along with clinical pharmacology data on levofloxacin exposure and natural history studies in AGM are adequate to file an application for treatment of plague.

Janssen submitted sNDAs for LEVAQUIN tablets on 27 Oct 2011 and for LEVAQUIN Injection and LEVAQUIN Oral Solution on 3 November 2011. The proposed indication is:

> LEVAQUIN is indicated for pneumonic plague following exposure to *Yersinia pestis* (*Y. pestis*) in adults and pediatric patients ≥6 months of age.

As discussed in Section 2.3 there are no FDA-approved antibacterials specifically indicated for the treatment of pneumonic plague (resulting from the direct inhalation of plague bacteria) due to the rarity of the natural human disease in the modern era and the paucity of antibiotic therapy studies conducted in appropriate animal models of disease. Further, there is an unmet medical need for the treatment of pediatric patients in the event of a plague outbreak and LEVAQUIN is approved for the treatment of inhalational anthrax (post-exposure) in children (<50 kg and ≥6 months of age). Based on fulfilling this core justification, Janssen requested a priority review of the sNDAs for the pneumonic plague indication. FDA granted priority review status on 27 December 2011.

2.5. Overview of the Pneumonic Plague Development Program

2.5.1. Development Under the Animal Rule

Because of ethical concerns and infeasibility, evaluation of the efficacy of levofloxacin in the treatment of pneumonic plague could not be conducted directly in humans and had to rely on the results of animal models.

In accordance with 21 CFR 314.610 (revised as of April 1, 2011) Approval Based on Evidence of Effectiveness from Studies in Animals (i.e., the Animal Rule) and as agreed in the follow-up General Advice correspondence to Janssen (see Section 2.4.2), FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of 21 CFR 314.610 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

- There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance (chemical, biological, radiological, or nuclear) and its prevention or substantial reduction by the product.
- The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.
- The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.
- The data on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allow selection of an effective dose in humans (21 CFR 314.610 (a)(1)-(4)).

Y. pestis, the agent of pneumonic plague, is a CDC Category A threat agent that could not ethically be administered to human volunteers for clinical studies.

The sponsor proposes that the AGM (*Chlorocebus aethiops*) model of pneumonic plague is a sufficiently well-characterized model for predicting the efficacy response to levofloxacin in humans and that data from the single GLP study conducted in AGMs and supporting information from the literature on the efficacy of levofloxacin in rodent models of plague infection provide the substantial evidence of effectiveness outlined in 21 CFR 314.610.

2.5.2. Natural History of *Yersinia Pestis* in Animals and Relevance to Human Progression

Three laboratories conducted studies to document the natural history of the pathogenesis of *Y. pestis* infection following aerosol exposure: United States Army Medical Research Institute of

Infectious Diseases (USAMRIID) (Frederick, Maryland, USA), the Lovelace Respiratory Research Institute (LRRI) (Albuquerque, New Mexico, USA), and the Battelle Biomedical Research Center (BBRC) (Columbus, Ohio, USA). These studies documented the natural history of the disease in telemetered animals and thus identified fever as a clinical sign or trigger for antibiotic intervention, and demonstrated that a levofloxacin dose that mimicked the human dose (500 mg once daily [QD]) could be administered. Collectively, these studies demonstrated that the pathogenesis and disease progression for *Y. pestis* were similar in AGMs and humans and showed that AGMs are an appropriate animal model for determining the potential efficacy of levofloxacin in the treatment of human plague.

Details of the studies of the natural history of *Y. pestis* in AGMs conducted by NIAID can be found in the briefing documents provided by FDA, and a summary is also provided in Attachment 1.

2.5.3. Pharmacokinetic Studies in African Green Monkeys

The absorption, distribution, metabolism and excretion (ADME) properties of levofloxacin were fully characterized in previously conducted studies in rodents, Cynomolgus and Rhesus monkeys. The information generated from these studies was used to support the original NDAs for NDA 20-634 (Oral tablet), NDA 20-635 (Injection) submitted to FDA on 21 December 1995, and NDA 21-721 (Oral solution) submitted to FDA on 19 December 2003. ADME studies in Rhesus monkeys were later conducted to support supplemental NDAs (S-027/NDA 20-634 and S-023/NDA 20-635) for an indication of inhalation anthrax (post-exposure) submitted to FDA on 24 January 2004; however, studies in AGMs were not conducted to support these NDAs. Therefore, additional pharmacokinetic (PK) studies were conducted in the AGM to support the pneumonic plague (post-exposure) indication.

The initial PK studies with levofloxacin in AGMs were conducted to evaluate pharmacokinetics and systemic exposure. Based on data from these initial exploratory PK studies, an IV dosing regimen designed to approximate human exposure, 8 mg/kg followed by 2 mg/kg 12 h later (8/2 mg/kg), was selected for the evaluation of the efficacy of levofloxacin in AGMs. However, as a very limited volume of monkey plasma was available from the efficacy study, only peak and trough levofloxacin plasma concentrations were determined. To supplement this exposure information from the efficacy study, the full PK profile of levofloxacin in AGMs using the 8/2 mg/kg humanized dosing regimen was determined in 2 separate studies. The resulting exposure data were compared to exposure data in humans treated with the intended clinical dose of 500 mg QD. Overall, the 8/2 mg/kg dosing regimen in AGMs resulted in a PK profile that, although lower than the targeted human exposure level, was sufficient for efficacy against AGM pneumonic plague.

Further details of the PK studies conducted in AGMs can be found in Section 3.2.2.2.

2.5.4. Efficacy Study in African Green Monkeys

A single, GLP efficacy study (Study FY07-070), sponsored by NIAID, was conducted by Lovelace Biomedical and Environmental Research Institute (LBERI) to investigate the efficacy

of post-exposure treatment with levofloxacin for established pneumonic plague in an AGM (*Chlorocebus aethiops*) model that mimicked human disease. Details of the methodology and results of the study are described in Section 3.2.2.4.

3. NONCLINICAL PHARMACOLOGY AND PHARMACOKINETICS

3.1. In Vitro Microbiology

3.1.1. In Vitro Susceptibility Testing

The in vitro activity of levofloxacin against *Y. pestis* has been evaluated in several studies comprising 600 *Y. pestis* isolates (Table 1). Based on the current Clinical and Laboratory Standards Institute (CLSI)[13] levofloxacin-susceptible breakpoint of ≤0.25 µg/mL, all *Y. pestis* isolates were susceptible to levofloxacin with minimum inhibitory concentrations (MICs) ranging from ≤0.015 to 0.12 µg/mL.

Published data pertaining to the in vitro susceptibility of *Y. pestis* to other fluoroquinolone agents include studies of ofloxacin (a racemic mixture which consists of 50% levofloxacin), ciprofloxacin, gatifloxacin, moxifloxacin, and trovafloxacin, and provide data that substantiates the overall good activity of fluoroquinolones against this pathogen with MIC_{50} and MIC_{90} values comparable to levofloxacin (Table 1).

The highest fluoroquinolone MIC reported in the aforementioned studies was for 1 isolate in which the ciprofloxacin MIC was 0.5 µg/mL using the broth dilution reference method which would make this isolate ciprofloxacin non-susceptible using the CLSI[13] susceptible breakpoint of 0.25 µg/mL; however, it should be noted that the ciprofloxacin MIC for the same isolate was 0.06 µg/mL by the non-reference Etest method.[36] From our search of the literature this was the only incidence in which clinical *Y. pestis* isolates may have been non-susceptible to a fluoroquinolone. This is in contrast to reports that have documented resistance to antibacterials recommended for therapy and prophylaxis of *Y. pestis* infections (chloramphenicol, streptomycin, sulfonamides, and tetracycline) as well as others including ampicillin, kanamycin, spectinomycin and minocycline.[23,25]

Table 1: In Vitro Susceptibility of *Y. pestis* to Levofloxacin and Other Fluoroquinolones

Country or Laboratory	Method	N	Drug	MIC (µg/mL)			Year[a] (Reference)
				MIC_{50}	MIC_{90}	Range	
USAMRIID	Broth dilution	30	Levofloxacin	0.03	0.06	0.008-0.12	NR[b] (Study RIID-YpLMIC-2005)
HPA	Broth dilution	12	Levofloxacin	0.03	0.06	≤0.015-0.06	NR (Study HPA-YpLMIC-2008)
Namibia	Agar dilution	100	Levofloxacin	<0.03	<0.03	<0.03-0.06	1982-1991 (Frean 1996)[20]
			Ofloxacin	<0.03	<0.03	<0.03-0.12	
Worldwide	Broth dilution	392	Levofloxacin	0.03	0.03	0.03-0.06	1940-2009 (Ulrich 2012)[56]
			Ciprofloxacin	0.03	0.03	0.03-0.12	
Anti-Plague Scientific Research Institute Russia	Agar dilution	40	Levofloxacin	NR	NR	0.01-0.02	NR (Ryzhko 2009)[52]
			Ofloxacin	NR	NR	0.04-0.08	
			Ciprofloxacin	NR	NR	0.01-0.02	
			Moxifloxacin	NR	NR	0.16-0.32	
USAMRIID and CDC	Broth dilution	26	Levofloxacin	NR	≤0.06	≤0.06-0.12	NR (Lonsway 2011)[36]
	Etest		Levofloxacin	NR	0.06	0.008-0.12	
	Broth dilution		Ciprofloxacin	NR	0.12	≤0.03-0.5	
	Etest		Ciprofloxacin	NR	0.06	0.008-0.12	
Vietnam	Agar dilution	78	Ofloxacin	0.12	0.25	0.031-0.25	1985-1993 (Smith 1995)[55]
			Ciprofloxacin	0.031	0.062	0.008-0.062	
French army collection	Agar dilution	94	Ofloxacin	<0.12	<0.12	<0.12-0.12	1964-1988 (Hernandez 2003)[29]
			Ciprofloxacin	<0.12	<0.12	<0.12-0.12	
			Gatifloxacin	<0.12	<0.12	<0.12-0.12	
Pasteur Institute	Agar dilution	18	Ofloxacin	0.12	0.12	0.06-0.12	NR (Bonacorsi 1994)[5]
Namibia	Agar dilution	28	Ciprofloxacin	0.016	0.031	0.016-0.031	1982-1991 (Frean 2003)[21]
UK	Broth dilution	8	Ciprofloxacin	NA[c]	NA[c]	<0.06-0.12	NR (Russell 1998)[50]
Ordway Research Institute	Broth dilution	30	Moxifloxacin	0.03	0.06	0.015-0.06	NR (Louie 2011)[38]
U.S.	Etest	92	Trovafloxacin	0.023	0.032	0.006-0.047	1977-1998 (Wong 2000)[60]

[a]Year in which isolates were identified
[b]NR, not reported
[c]NA, not applicable

3.1.2. In Vitro Hollow-Fiber Infection Model

Data from an in vitro pharmacodynamic, hollow-fiber infection model conducted with *Y. pestis* also supports the efficacy of levofloxacin in plague treatment.[37] In this study, the relative activities of 10-day regimens of streptomycin and levofloxacin were directly compared including evaluation of the emergence of resistance using conditions that simulate the human serum concentration time profiles for standard clinical regimens of 1 g of streptomycin given every 12 hours and 500 mg of levofloxacin given every 24 hours. In the model, untreated bacteria grew from 10^7 to 10^{10} colony forming units (CFU)/mL. Streptomycin therapy resulted in a 10^5 CFU/mL reduction in the number of viable bacteria over 24 hours, followed by re-growth of streptomycin-resistant mutants. In contrast, levofloxacin resulted in a $>10^6$ CFU/mL reduction in the number of viable bacteria within 12 hours, and ultimately sterilized the culture without resistance selection. In additional studies, streptomycin-resistant and wild-type variants of *Y. pestis* were determined to exhibit equal fitness in both immune normal and neutropenic mouse thigh infection models. In contrast, 90% of levofloxacin-resistant isolates, cultured from the hollow fiber control arm, did not proliferate in the mouse thigh infection models and were shown to be less fit than streptomycin-resistant and wild-type *Y. pestis*. In conclusion, levofloxacin was judged to be superior to streptomycin in this in vitro infection model by both bactericidal and resistance development criteria at human equivalent doses.[37]

3.2. In Vivo Animal Models of Plague Infection

3.2.1. Rodent Models of Plague

In animal studies of plague disease, ofloxacin (a racemic mixture which consists of 50% levofloxacin) has been reported to be efficacious in both rodent[5,7,2,53] and primate[49] models of *Y. pestis* infection. In specific investigations of levofloxacin, several reports have described efficacy in rodent models of primary pneumonic plague. In one study, 60 mice were infected with an inoculum corresponding to an inhaled dose of 20 to 25 times the 50% lethal dose (LD_{50}) of *Y. pestis* by whole-body aerosol and treated with levofloxacin 24 h post challenge at doses from 1.5 to 15 mg/kg every 12 h (10 mice per levofloxacin dose group); levofloxacin completely protected normal mice at doses as low as 1.5 mg/kg every 12 h (or 3 mg/kg/day) and completely protected neutropenic mice out to the termination of the experiment on Day 23 at a dose of 15 mg/kg given every 12 hours (RIID-YpEff-2006).[27] In a second series of studies in which mice were infected via nasal instillation of 5 LD_{50} of *Y. pestis,* a total of 200 mice were treated with levofloxacin doses ranging from 0.05 to 150 mg/kg/day (10 mice per dose group). Complete protection was achieved with doses of levofloxacin equal to or greater than 5 mg/kg/day (Study UTMB-YpEff-1-8).[48] In a rat model of pneumonic plague also infected intranasally with $\geq$12 LD_{50} *Y. pestis*, a total of approximately 70 rats were treated with levofloxacin 24 h post-infection at doses of 0.5 to 20 mg/kg/day (with dose groups ranging from 6 to 9 rats); levofloxacin completely protected rats at doses as low as 5 mg/kg/day (Study UTMB-YpEff-1-8). A delay in the initiation of levofloxacin treatment significantly increased mortality in the mouse and rat infection models, with approximately 10% of mice, and 44% of rats surviving levofloxacin treatment (5 or 10 mg/kg/day doses) administered 48 h post-infection (Study UTMB-YpEff-1-8).

3.2.2. African Green Monkey Model of Plague

3.2.2.1. Natural History of Pneumonic Plague in African Green Monkeys and Humans

A series of studies were sponsored by NIAID to characterize the clinical course of pneumonic plague in untreated AGMs. The description of the methodology and results of these studies is included in the FDA briefing materials provided in preparation for the Center for Drug Evaluation and Research Anti-Infective Drugs Advisory Committee Meeting on 3 April 2012, and for completeness can also be found in Attachment 1 of this briefing document. A comparison of the natural course of pneumonic plague in humans and AGMs is also provided.

3.2.2.2. Pharmacokinetics in African Green Monkeys

3.2.2.2.1. Absorption and Pharmacokinetics

Levofloxacin was rapidly absorbed after oral administration to AGMs, with C_{max} and AUC values noted to increase in a dose-dependent or dose-proportional manner, respectively. No significant differences were noted in PK parameters between monkeys given single or repeated IV levofloxacin doses. The IV plasma half-life ($t_{1/2}$) of levofloxacin in AGMs was short (3.3 h), and p.o. bioavailability (F) was high (80%).

Based on the results from the initial study, a second PK study in AGMs was conducted with a dose of 8 mg/kg administered via a 30-min IV infusion, followed 12 h later by a second 30-min IV infusion of 2 mg/kg (i.e., 8/2 mg/kg IV) in order to mimic systemic exposure in humans (Study FY08-150). A confirmatory GLP PK study in AGMs (Study B465-10) was also conducted with the same humanized dosing regimen. The PK profiles of the humanized dosing regimen were similar in the 2 PK studies. The average C_{max} (3.3 µg/mL) and AUC_{0-24h} (11.9 µg·h/mL) values for the humanized dose in AGMs (Table 2) were lower than those in humans administered 500 mg IV once daily (6.2 µg/mL and 48.3 µg·h/mL, respectively).

Information on the study design and results is provided in Table 2.

Table 2: Mean Pharmacokinetic Parameters Following Single or Repeat Doses of Levofloxacin in African Green Monkeys[a]

Study Type/ (Study No.)	N	Route	Duration	Dose (mg/kg)	C_{max} (µg/mL)	t_{max} (h)	Vz or Vz/F (mL/kg)	$AUC_{(0-\infty)}$ (µg·h/mL)	$t_{1/2}$ (h)	Cl or CL/F (mL/h/kg)	F (%)
Single and Repeat-Dose PK (Study B122-03)[b]	3/sex[b]	p.o.	once (SDE)	15	5.00 (3.24)	1.50 (0.77)	3317.48 (947.27)	24.16[d] (5.99)	4.74 (1.75)	504.32 (92.48)	80
		p.o.	once (SDE)	20	5.22 (1.65)	1.50 (0.77)	4084.37 (540.23)	32.56 (5.74)	5.77 (1.19)	503.54 (88.46)	80
		p.o.	once (SDE)	25	5.82 (1.26)	2.60 (1.33)	3145.57 (509.47)	36.01 (6.17)	4.24 (1.09)	528.38 (78.80)	74
		IV (20-min inf)	once	15	13.36 (2.86)	0.33 (0.00)	2334.88 (216.48)	30.55 (5.30)	3.30 (0.65)	503.89 (90.19)	NA
		IV (20-min inf)	14 days (1st dose)[c]	20	16.92 (1.48)	0.30 (0.07)	2570.44 (125.68)	45.35 (8.23)	3.21 (0.44)	566.99 (106.04)	NA
		IV (20-min inf)	14 days (last dose)[c]	20	11.83 (1.78)	0.25 (0.09)	3036.95 (521.34)	30.44 (4.26)	2.52 (0.31)	836.34 (130.07)	NA
Single Dose PK (Study FY08-150)[f]	3 F	IV (30-min inf)	Once	8	3.17 (0.24)	0.09 (0.01)	3559 (729)	8.86 (2.01)	2.65 (0.15)	932 (191)	NA
		IV (30-min inf)	Once	2	0.71 (0.60)	12.87 (0.24)	4167 (NC)[e]	3.58 (NC)[e]	5.17 (NC)[e]	582 (NC)[e]	NA
Single Dose PK (Study B465-10)[f]	3M	IV (30-min inf)	Once	8	3.25 (0.36)	0.60 (0.01)	1980 (300)	10.30[g] (2.33)	2.36 (0.44)	602.15 (179.28)	NA
	3 F	IV (30-min inf)	Once	8	3.34 (0.21)	0.60 (0.01)	2300 (110)	7.95[g] (0.69)	2.01 (0.01)	793.83 (37.93)	NA
	3M	IV (30-min inf)	Once	2	0.90 (0.22)	12.80 (0.1)	2500 (710)	3.53[h] (1.33)	2.81 (0.61)	661.62 (340.76)	NA
	3 F	IV (30-min inf)	Once	2	0.72 (0.10)	12.60 (0.01)	3600 (690)	2.04[h] (0.32)	2.57 (0.17)	964.32 (130.89)	NA

[a] Values in parentheses are standard deviation.
[b] Study B122-03 consisted of 3 phases; monkeys (3/sex) were re-used at each dose and study phase. In Phase I, monkeys received single escalating p.o. (nasogastric) doses of 15, 20, and 25 mg/kg on Days 1, 15 and 29, respectively, with a 2-week washout period between doses. In Phase II, monkeys received a single 20-minute IV infusion of 15 mg/kg on Day 43, and in Phase III, monkeys received repeated 20-minute IV infusions of 20 mg/kg for 14 days, from Day 85 to Day 98.
[c] PK values are shown for Phase III of Study B122-03 for the first (Day 85) and last (Day 98) of 14 days of IV doses. Values shown are for total drug.
[d] $AUC_{0\text{-}8\ h}$
[e] N=2.
[f] Monkeys (3 F) in Study FY08-150 and in Study B465-10 (3/sex) were administered a 30 minute IV infusion of 8 mg/kg levofloxacin followed by a dose of 2 mg/kg 12 hours later.
[g] $AUC_{0\text{-}12\ h}$
[h] $AUC_{12\text{-}24\ h}$
F = female; h = hours; inf. = infusion; IV = intravenous; min = minutes; N = number; NA = not applicable; NC = not calculable; No. = number; p.o. = oral; SDE = single dose escalation

3.2.2.2.2. Plasma Protein Binding

The plasma protein binding of levofloxacin in the plasma of AGMs ranged from 15 to 32% (mean: 25%) at concentrations of 0.34 to 2.48 µg/mL. These values were not significantly different from those observed in other nonclinical species (rats, dogs, monkeys) and humans (11 to 38%) at concentrations of 1 to 10 µg/mL.[19,28]

3.2.2.2.3. Metabolism/Excretion

The metabolic fate of levofloxacin has not been investigated in AGMs. However, the metabolism and excretion of levofloxacin has been investigated following p.o. dosing in the rat, dog, Cynomolgus and Rhesus monkeys, and humans.[16,28]

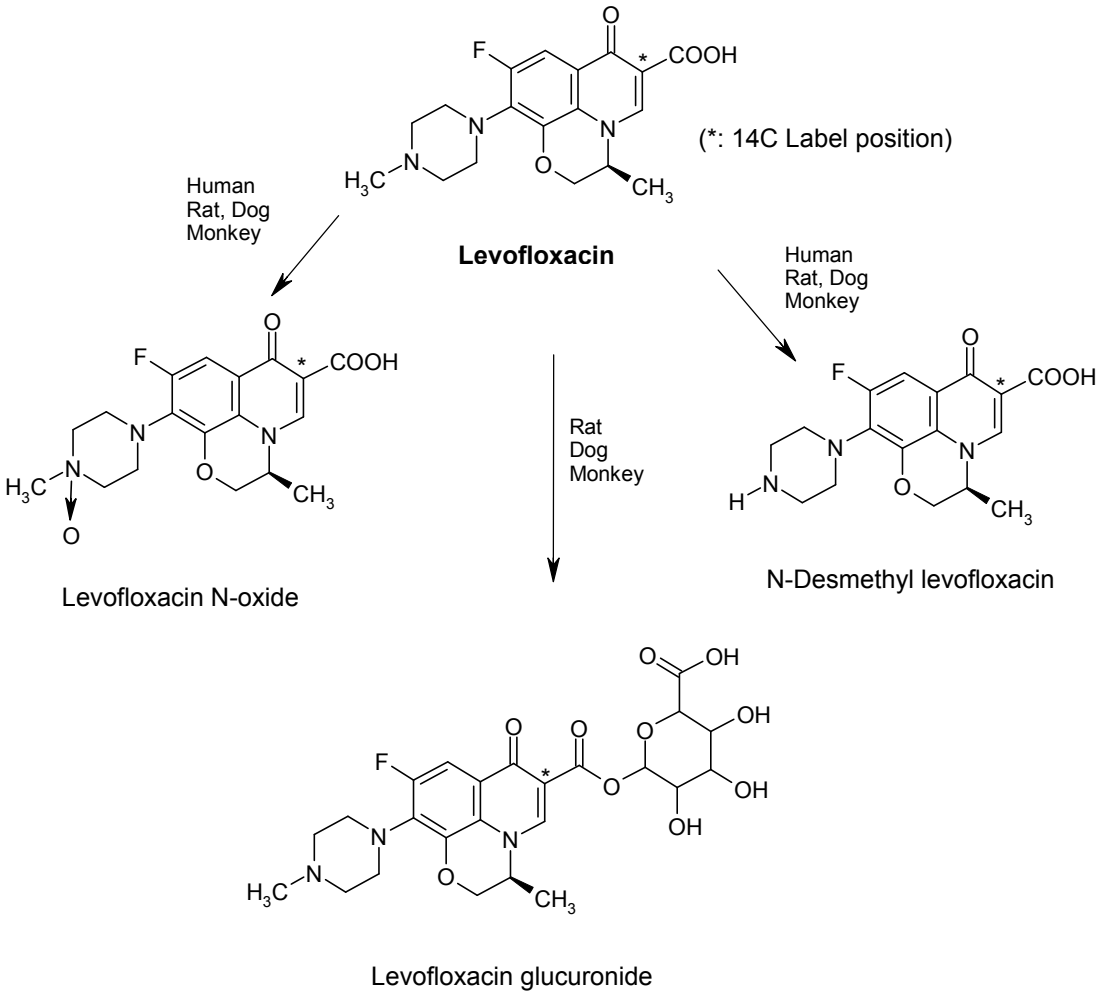
Levofloxacin undergoes minimal metabolism in dogs, monkeys and humans. Unchanged levofloxacin accounted for 90% of drug-related substance in dog and monkey serum. In humans, plasma levels of levofloxacin metabolites accounted for only 1-2 % of parent drug, with less than 5% of the administered levofloxacin excreted in the urine as metabolites in 24 h, whereas approximately 80% of the dose was excreted in urine as unchanged drug in 48 h.[19]

Overall, >70% of the unchanged parent drug was excreted in urine and feces of rats, dogs and monkeys. In humans, approximately 80% of the unchanged parent drug was excreted in urine,[19] indicating across species the metabolism of levofloxacin was minimal.

Minimal metabolism was observed in non-rodent species; however, levofloxacin-ß-glucuronide (M1) was detected as a major metabolite in the rat with 25% of the total drug related substance in serum (12% of the dose in urine). A minor metabolite, desmethyl levofloxacin (M2; 8.9% of the dose in urine), was also observed in rats following repeated dosing.[16] In contrast, M1 was a minor metabolite in plasma, accounting for <3% of drug related substances in plasma and only <0.4% of the dose in Rhesus monkeys. M1 and 2 other minor metabolites, i.e., M2 and levofloxacin N-oxide (M3) were detected as minor metabolites in Cynomolgus and Rhesus monkeys (each <5% of the total dosed radioactivity).

The metabolic fate of levofloxacin in the Cynomolgus and Rhesus monkeys is similar to that in humans, except that M1 was detected as a minor metabolite in monkeys but was not detected in humans (Figure 2). Given the limited and similar metabolism of levofloxacin among Cynomolgus monkeys, Rhesus monkeys and humans, and the similarities in levofloxacin pharmacokinetics between Rhesus and AGMs, it is very unlikely that a unique metabolite would be formed in AGMs.

Figure 2: Metabolism of Levofloxacin Across Species



3.2.2.3. Dose Justification

3.2.2.3.1. Levofloxacin Exposure in African Green Monkeys and Adult Humans

Levofloxacin PK in humans and AGMs has been extensively evaluated. In adult humans, levofloxacin has a plasma $t_{1/2}$ of approximately 6 to 8 h, and is mainly excreted as unchanged drug in the urine. Levofloxacin plasma concentrations exceeded the minimum inhibitory concentration (MIC) against *Y. pestis* for the entire dosing interval at the 500 mg IV QD human dose (Table 3). In contrast, levofloxacin has a shorter $t_{1/2}$ (approximately 3 h) in AGMs. Since the $t_{1/2}$ of levofloxacin in AGMs is shorter than in adult humans, a humanized dosing regimen, which would provide systemic exposure more similar to adult humans, was considered for use in the AGM efficacy study.[45] AGMs were treated with a humanized dose regimen (8/2 mg/kg), which provided a maximum plasma concentration of 3.3 µg/mL, far below adult human plasma C_{max} (6.2 µg/mL) and an average of only 25% of the adult human plasma AUC value of 48.3 µg·h/mL (Table 3). Additionally, throughout the 24 h dosing period, the plasma concentrations of levofloxacin in the AGM did not exceed that in adult human at the 500 mg IV or oral QD dose.

Table 3: Comparison of Levofloxacin Pharmacokinetic Parameters in Adult Human and African Green Monkey

Species	IV Dose	AUC/MIC$_{100}$ Ratio[a]	C_{max} (µg/mL)	% Human C_{max} (500 mg)	$AUC_{0\text{-}24\ h}$ (µg•h/mL)	% Human AUC (500 mg)	Trough Conc. (µg/mL)
Adult Human Volunteer[d]	500 mg IV QD Single	402	6.2	NA	48.3	NA	0.5
Adult Human Volunteer[d]	500 mg IV QD Multiple	455	6.4	NA	54.6	NA	0.6
African Green Monkey (Study B465-10)	8/2 mg/kg IV[b] Single	99	3.3	53	11.9	25%	<0.03-0.06[c]

[a] MIC_{90} values determined for levofloxacin against sets of *Y. pestis* isolates (n = 12 to 392) range from <0.03 to 0.06 µg/mL (see Table 1 in Section 3.1.1) . The MIC_{100} value of 0.12 µg/mL reflects the highest levofloxacin MIC value observed across all species and was used for the AUC/MIC_{100} calculation.
[b] First dose 8 mg/kg, followed by a second dose of 2 mg/kg 12 h later.
[c] Trough concentration in females and males.
[d] Data from approved LEVAQUIN USPI (see Attachment 2)
AUC = area under the curve; NA = Not applicable; QD = once daily

Since levofloxacin was administered for 10 days in the efficacy study in AGMs (Study FY07-070), the effect of repeated dosing must also be considered. In a separate study (Study B122-03), repeated IV dosing of 20 mg/kg levofloxacin to AGMs for 14 days increased the clearance of levofloxacin, which resulted in a decreased levofloxacin AUC by approximately 30% (Table 2). Thus, the results in the repeat dosing PK study further support lower systemic exposure to levofloxacin in the AGM efficacy study compared to a 500 mg QD IV dose in adult humans.

3.2.2.3.2. Levofloxacin Exposure in Pediatric Subjects

The PK of levofloxacin has also been evaluated in the pediatric population.[10,35] Three single-dose, multicenter, pharmacokinetic studies were conducted in 85 children in 5 age groups: 6 months to <2 years, 2 to <5 years, 5 to <10 years, 10 to <12 years, and 12 to 16 years. Each child received a single 7 mg/kg dose of levofloxacin (not exceeding 500 mg) either IV or orally. Plasma samples were collected through 24 hours after dosing. Pharmacokinetic parameters were estimated and compared among the 5 age groups and to previously-collected adult data. The results showed levofloxacin absorption and distribution in children are not age-dependent and are comparable to those in adults. Levofloxacin elimination (reflected by $t_{1/2}$ and clearance), however, is age-dependent. Children younger than 5 years of age clear levofloxacin nearly twice as fast (IV dose, 0.32±0.08 L/h/kg; oral dose, 0.28±0.05 L/h/kg) as adults and, as a result, have an AUC approximately one-half that of adults.[10]

To mimic pediatric levofloxacin exposures to adult humans, PK data from Chien's study[10] in pediatric subjects and 2 studies of 47 healthy adults receiving 500 and 750 mg levofloxacin were used for pharmacometric analyses.[35] Body weight was found to be a significant covariate for levofloxacin clearance and volume of distribution. Consistent with the developmental physiology, clearance was found to be reduced in pediatric patients under 2 years of age due to immature renal function. Different dosing regimens in children were simulated to match adult

exposure (AUC from 0 to 24 h, C_{max} and C_{min} in serum at steady state) following the approved adult dose of 500 mg QD. The results showed that the pediatric dose of 7.5 mg/kg every 12 hours would provide 84-98% of the C_{max} and 92-102% of the AUC in adult humans (Table 4).[35] In addition, during the 24-hour dosing period, the trough concentration (0.6 µg/mL) would be much higher than the MIC of *Y. pestis* (0.12 µg/mL) (Table 4).

Table 4: Comparison of Levofloxacin Exposures in Pediatric and Adult Subjects

Age Group	AUC/MIC_{100}[a] Ratio	C_{max} (µg/mL)	% Adult Human C_{max} (500 mg)	$AUC_{0\text{-}24\ h}$ (µg•h/mL)	% Adult Human AUC (500 mg)	Trough Conc. (µg/mL)
Pediatric Subjects [35]						
6 mo to <2 yr	431	5.6	88	51.7	95	0.6
2 to <5 yr	417	5.4	84	50.0	92	0.6
5 to <10 yr	463	5.4	84	55.6	102	0.9
10-18 year	464	6.3	98	55.7	102	0.6
Adult Human Volunteer[b]	455	6.4	NA	54.6	NA	0.6

Note: The dosage regimen assessed in pediatric subjects was 7.5 mg/kg Q12h for children <50 kg and 500 mg QD for children >50 kg. The adult dose was 500 mg QD.

[a] The MIC_{100} value of 0.12 µg/mL reflects the highest levofloxacin MIC value observed across all species and was used for the AUC/MIC_{100} calculation.
[b] Data from approved LEVAQUIN USPI (see Attachment 2)

The pharmacometric analyses demonstrated that renal function in clearing levofloxacin was not mature until 2 years of age; after that, body weight is the only factor that affects levofloxacin clearance. These analyses were designed to meet the target exposure predicted by animal experiments at the same time that they considered the risks of using doses of levofloxacin that best approximated exposures in adults.[35] Taken together, these considerations have led to the conclusion that the recommended dosage regimen for children <50 kg is 8 mg/kg Q12h and for children weighing ≥50 kg is 500 mg QD. The recommended pediatric dosage regimens are expected to match the exposure of the 500 mg QD dose approved for adults, and therefore are also expected to demonstrate efficacy in children comparable to that observed in adults.

3.2.2.3.3. Levofloxacin Pharmacokinetics and Exposure in the Efficacy Models

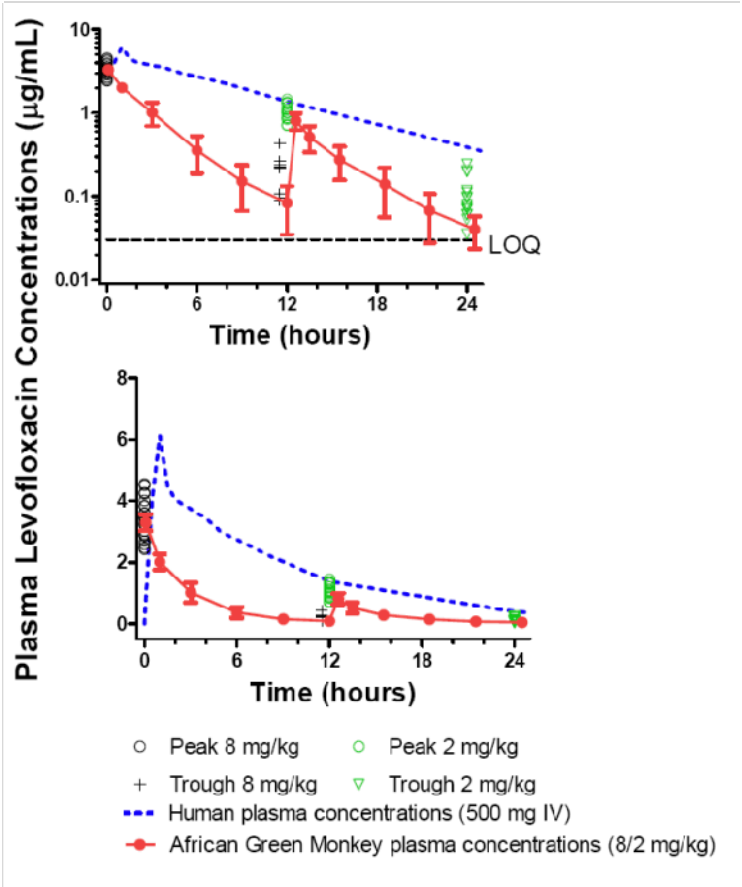
3.2.2.3.3.1. Levofloxacin Pharmacokinetics and Exposure in the African Green Monkey

Plasma drug concentrations were also monitored in the efficacy study in AGMs (Study FY07-070). The objectives of the plasma concentration monitoring in the efficacy study was to demonstrate that plasma concentrations in the diseased monkeys were similar to those observed in healthy monkeys and did not exceed those observed in humans using approved doses through the duration of treatment.

The plasma levofloxacin concentrations in the treated animals from Cohort 1 and 2 were not interpretable; however, the values from Cohort 3 align well with the data generated in the 24 h PK study in healthy animals (Study B465-10; see Figure 3). Peak concentrations averaged approximately 3.3 ± 0.82 µg/mL following the first and third doses (30-min infusion of 8 mg/kg

levofloxacin). In the PK study in healthy animals (B465-10), mean peak concentrations were 3.3 ± 0.27 µg/mL. Mean peak concentrations following the 2 mg/kg dose were 1.08 µg/mL in the efficacy study and 0.81 ± 0.18 µg/mL in the PK study. Trough concentrations following the 2 mg/kg dose averaged 0.07 ± 0.03 µg/mL in the efficacy study, and ranged from <0.03 to 0.06 µg/mL in the PK study. Plasma drug concentrations were consistent with those observed in the exploratory pharmacokinetic study and the highest Cmax recorded in any nonhuman primate on any day of the efficacy study was 53% of the reported human C_{max} for levofloxacin.

Figure 3: Comparison of Plasma Levofloxacin Concentrations Following Intravenous Dosing in African Green Monkeys and Humans



Note: Upper figure log scale, lower figure linear scale:
Label The blue dashed line represents the observed concentrations following a dose of 500 mg levofloxacin in healthy human volunteers. The red line represents the average plasma levofloxacin concentrations in healthy African Green monkeys following doses of 8 mg/kg and 2 mg/kg in PK study (B465 10). The black and green symbols are peak and trough levels from Cohort 3 of the efficacy study (FY07-070; all dosing days).

3.2.2.3.3.2. Levofloxacin Pharmacokinetics and Exposure in the Mouse

The systemic exposure of levofloxacin was also reported in 2 mouse models of pneumonic plague. Intraperitoneal (i.p.) treatment of levofloxacin to female Swiss Webster mice at 5 mg/kg dose resulted in 100% protection against pneumonic plague. The $AUC_{0-\infty}$ at the 5 mg/kg i.p. dose was 16.7 µg·h/mL.[48] In a female BALB/c mouse model, treatment of levofloxacin at 15 mg/kg every 12 h also resulted in 100% protection of pneumonic plague. The AUC_{0-24h} after 15 mg/kg every 12 h was 30 µg·h/mL.[27]

3.2.2.3.3.3. Summary of Levofloxacin Pharmacokinetics and Exposure in Efficacy Models

In the AGM and mouse efficacy models, the systemic exposures of levofloxacin at efficacious doses were much lower than the AUC (48.3 μg·h/mL) in humans at the 500 mg IV QD dose. Additionally, the plasma levofloxacin concentrations in humans during the 24-hour treatment period were much higher than the MIC for *Y. pestis* (0.12 μg/mL). Therefore, the lower than human exposure of levofloxacin suggests the efficacious treatment of pneumonic plague with levofloxacin in animal models is relevant to the treatment for humans.

3.2.2.4. Efficacy of Levofloxacin in African Green Monkeys with Pneumonic Plague (Study FY07-070)

A single study was performed with the objective of testing the efficacy of levofloxacin for treatment of pneumonic plague in AGMs and some of the results were recently published.[33] This study was performed in compliance with GLP requirements, with the exception of a few analyses noted below. A total of 24 research-naïve animals, that were determined by a laboratory animal veterinarian, the principal investigator and the study director to be in acceptable health according to the health screening methods outlined in the protocol, were placed on study in 3 cohorts. Seven animals were assigned to the control group (Group 1) and 17 animals to the levofloxacin-treated group (Group 2). Aerosol challenges were carried out on 3 different days (i.e., Cohorts 1, 2, and 3), and animals in both the control and levofloxacin-treated groups were challenged on each day according to the design in Table 5. In addition to the 24 animals described above, 2 additional animals originally randomized to Cohort 2 were removed from study; AGM X717 was removed from study prior to challenge with *Y. pestis* due to health reasons and AGM X779 was removed from study after challenge due to initiation of treatment prior to becoming febrile.

Table 5: Efficacy Study Design (Study FY07-070)

	Cohort (Date of *Y. pestis* Challenge)			
	Cohort 1 (3/25/2008)	Cohort 2 (5/2/2008)	Cohort 3 (1/23/2009)	Total
Control (Group 1)	3	2	2	7
Levofloxacin (Group 2)	5	4	8	17

Animals were approximately 3 to 7 kg and adults (>2 years old) when put on study, though the exact age of animals is unknown. Prior to challenge, animals had telemeters surgically implanted and Broviac (Cohorts 1 & 2) or Hickman (Cohort 3) catheters inserted. Baseline physiological data were collected for 7 days prior to challenge. Additionally, blood was collected as a baseline for arterial blood gases (not validated), levofloxacin levels, quantitative bacteriology, clinical chemistry, coagulation indices, and hematology. Body weight was also obtained pre-challenge. Transthoracic echocardiography (not validated) was performed on 2 levofloxacin-treated animals each from Cohort 1 and Cohort 2.

The *Y. pestis* CO92 challenge material was freshly prepared from the same seed culture bank and using the same procedures as the FY06-126 natural history study conducted at LBERI (see Attachment 1).

Animals were anesthetized on Day 0, weighed, and a chest radiograph (not validated) was obtained prior to challenge. Each animal was exposed to the *Y. pestis* aerosol in a head-only chamber in a Class III biosafety cabinet, with a target dose of 100 ± 50 LD_{50}. Minute volume (i.e., the total volume of air that moves in and out of the lungs in 1 minute) was measured by whole-body plethysmography in real time during the challenge. Each animal's actual challenge dose was verified retrospectively by collecting the aerosol during the challenge in an all glass impinger and quantifying organisms by plating dilutions.

After challenge, clinical observations were recorded twice daily along with continuous telemetry monitoring. Blood was obtained daily for bacteremia, assessed quantitatively by serial dilution and plating on tryptic soy agar. Blood was drawn on Days 2 and 6 for hematology and clinical chemistry, and at moribund euthanasia for arterial blood gases and coagulation indices. Echocardiography was performed on Days 2-5, prior to moribund euthanasia (if possible) and on Day 14 and 27. A chest radiograph was obtained on Day 5 or at moribund euthanasia. All animals were necropsied, at time of death/moribund euthanasia, or scheduled necropsy at the end of the study on Day 28.

At the onset of a fever, defined as a mean temperature greater than 39°C for more than 1 hour with monitoring sessions every 4-6 hours, control and test article infusions began. Infusions occurred twice daily for 30 ± 5 minutes. The treatment group, Group 2, received levofloxacin at 8 mg/kg body weight followed by 2 mg/kg 12 ± 0.5 hours later, repeating this alternating dose regimen daily, for a total of 20 infusions. Control animals, Group 1, received similar volumes of 5% dextrose. Blood was drawn for peak and trough drug levels according to the following schedule: after the 1st infusion, before and after the 3rd infusion, after the 4th infusion, before and after the 6th infusion and before and after the 19th infusion.

The average challenge dose for each of the 3 cohorts was 74 ± 31 LD_{50}, 124 ± 10.5 LD_{50}, and 22 ± 23.1 LD_{50}, respectively. Individual challenge doses are presented in Table 6. The majority of challenge doses were within the target range (100 ± 50 LD_{50}) on the first and second challenge days (Cohorts 1 and 2), with the exception of animal X437 (Group 2, levofloxacin-treated) that received a challenge dose of 40 LD_{50}. On the third challenge day (Cohort 3), the starting nebulizer concentrations were 0.3 to 0.7 log lower than the concentration required to achieve the target aerosol concentration, resulting in lower challenge doses overall. Additionally, Cohort 3 animals fell into 2 groupings based on challenge order and challenge dose: 38 to 62 LD_{50} comprising 4 AGMs (Y283, Y293, X888, Y217) and 3 to 12 LD_{50} comprising 6 AGMs (Y295, Y276, Y301, Y160, Y226, Y275). This grouping coincides with a change in personnel after the first 4 AGMs (with higher exposures) were challenged with aerosolized *Y. pestis*. It is hypothesized that a dilution error may have occurred when the actual aerosol samples were enumerated after the challenge for these last 6 AGMs, as the pre-aerosol nebulizer concentrations for all 10 AGMs in this cohort were comparable. However, whether or not the lower exposure in

the latter group of 6 AGMs was real or perceived, it should be noted that all 10 AGMs in Cohort 3 became febrile and bacteremic with *Y. pestis* isolated from blood samples prior to the first infusion of levofloxacin or control article.

The decision to euthanize an AGM was based on the animal meeting at least 2 of the following 4 prospectively defined criteria: 1) respiratory rate by telemetry >60 respirations/min, 2) heart rate and ECG by telemetry >200 beats/min or abnormal repolarization signals (persistently inverted T waves or depressed ST segment) or significantly reduced depolarization amplitude, 3) observation of deep labored breaths with obvious excessive work of breathing, and 4) observation of any seizures OR too weak to climb onto perch or falling off perch OR constant hunched posture and unresponsive to stimulation and refusal to eat any offered food. Personnel (Principal Investigator / staff veterinarian) making euthanasia decisions were blinded to the animal's treatment group.

Table 6: Levofloxacin Efficacy Challenge Dose, Survival, Fever and Bacteremia Observations (Study FY07-070)

Animal ID	Treatment Group[a]	Challenge Day Cohort[b]	Sex	Challenge Dose, LD_{50}	1st Bacteremia day[c]	Time to Fever (hrs)	Outcome[d]	Time to Death, hours[e]	Terminal *Y. pestis* blood counts[f] (CFU/mL)
X702	1	1	F	56	4	93.4	D	119	$3.0x10^5$
X773	1	1	M	143	4	65.4	EU	114	$1.1x10^4$
X762	1	1	M	76	3	74.6	EU	122	$3.0x10^5$
U193	1	2	F	121	3	58.6	EU	86	$3.0x10^5$
X734	1	2	M	145	2	58.0	D	86	$3.9x10^{4g}$
X888	1	3	F	44	4	73.3	D	109	$1.5x10^{4g}$
Y283	1	3	M	47	3	68.2	D	106	$3.0x10^5$
X663	2	1	F	66	--	59.8	S		$3.3x10^0$
X662	2	1	F	81	3	67.9	S		BDL[h]
X648	2	1	F	57	3	70.4	S		$6.7x10^0$
X437	2	1	M	40	5	124.1	S		BDL
X523	2	1	M	75	2	52.8	S		BDL
X732	2	2	F	124	--	70.9	S		BDL
X419	2	2	F	120	--	61.1	S		BDL
X771	2	2	M	118	3	74.9	S		BDL
X761	2	2	M	118	--	70.0	S		BDL
Y160[i]	2	3	F	6	3*	65.0	EU	215	BDL
Y217	2	3	F	38	3	71.6	S		BDL
Y226[i]	2	3	F	12	3	66.3	S		BDL
Y295[i]	2	3	F	3	3*	125.0	S		BDL
Y275[i]	2	3	M	4	4	92.5	S		BDL
Y276[i]	2	3	M	3	7	165.3	S		BDL
Y293	2	3	M	62	--**	73.1	S		BDL
Y301[i]	2	3	M	3	3	67.8	S		BDL

[a] Group 1 = controls; Group 2 = levofloxacin-treated

[b] Animals were randomly assigned to 1 of 3 cohorts, challenged on 1 of 3 different days; Cohort 1 was challenged on 3/25/2008, Cohort 2 was challenged on 5/2/2008, Cohort 3 was challenged on 1/23/2009.

[c] -- = negative in quantitative assay on study days sampled; * Bacteremia detected in pre-infusion sample, not daily sample (For Cohort 3 only, blood was collected for post-challenge quantitative and qualitative bacteriology immediately prior to first infusion.); **A single *Y. pestis* colony was detected in a qualitative assay, pre-infusion.

[d] D = Found dead; EU = Euthanized; S = survived until end of Study, Day 28

[e] excluding scheduled euthanasia on Day 28 (667-675 hours)

[f] *Y. pestis* blood counts at death or terminal euthanasia(CFU/mL) or if sample not available at death, then last daily blood count prior to death is shown

[g] terminal blood sample not available; the blood count shown is from last daily blood draw prior to death

[h] BDL = below detection limit

[i] AGMs from Cohort 3 that had a low (3 to 12 LD_{50}) *Y. pestis* challenge dose

All 7 control animals (Group 1) became bacteremic (5 animals were bacteremic prior to the first infusion of control agent and the remaining 2 animals became bacteremic after the first infusion of control agent), demonstrated a fever on Days 2-4, and died on Day 4 or 5. Four of the control animals died naturally and 3 were euthanized in moribund condition. Five of the 7 control animals had terminal bacteremia at levels consistent with those reported in the natural history studies; a terminal blood sample was not obtainable from 2 control animals (X888, X734) that died, but the last daily blood draw prior to death also showed bacteremia levels similar to those

reported in the natural history studies. For all control animals, once they became bacteremic they remained bacteremic at each daily blood draw until death or moribund euthanasia.

Of the 17 levofloxacin-treated (Group 2) animals, 16 survived (Table 6). Thirteen of the animals were bacteremic prior to treatment with 12 animals having *Y. pestis* bacteremia detected using a quantitative assay and 1 animal (Y293) having bacteremia detected using a qualitative assay that yielded a single *Y. pestis* colony. Once treatment with levofloxacin was initiated bacteremia was negative by the next daily blood draw in every animal. At terminal necropsy 1 of these 13 animals (X648) had *Y. pestis* detected in the blood at very low levels (6.7 CFU/mL) even though no *Y. pestis* isolates were found in numerous blood samples take during the treatment and post-treatment observational phases of the study and the animal was afebrile prior to euthanasia. Four animals did not become bacteremic after *Y. pestis* exposure. Three animals (X732, X419, X761) never tested positive for *Y. pestis* in either blood or tissues; the fourth animal X663 had a very low level of *Y. pestis* (3.3 CFU/mL) in the blood at terminal necropsy even though no *Y. pestis* isolates were found in numerous blood samples taken during the treatment and post-treatment observational phases of the study and the animal was afebrile prior to euthanasia. Among all 17 animals, 2 had *Y. pestis* isolated from tissues at terminal necropsy: X648 had $1.8x10^2$ CFU/g of *Y. pestis* in lung tissue; X523 had $3x10^2$ CFU/g of *Y. pestis* in lung tissue. These animals were afebrile prior to the scheduled sacrifice so the significance of these observations is unknown.

The levofloxacin-treated animal (Y160) that did not survive was euthanized on Day 9 after severe vomiting. Microscopic findings of the stomach of this animal revealed marked neutrophilic or mixed inflammatory infiltrates and marked edema. The etiology of the stomach lesion and any relationship to treatment is unknown. This animal was bacteremic on Day 3 (pre-infusion blood sample) and all subsequent blood samples and terminal tissue samples were negative for *Y. pestis*. This animal also survived twice as long as the control animals (215 hours vs. an average of 106 hours for Group 1 controls) and its fever had resolved prior to euthanasia although the diurnal pattern was disrupted. Importantly, there was a trend toward resolution of the pulmonary pathology seen in this animal.

A complete gross necropsy was performed on all animals at death or scheduled/moribund euthanasia. Gross necropsy observations were recorded. Photographs were used to document unusual or characteristic lesions. Whole blood was collected, if possible, for quantitative bacteriology with any remaining serum stored frozen. The following tissues were collected for quantitative bacteriology and a portion was fixed in 10% neutral buffered formalin for histopathology evaluation: lung (lesion and non-lesion), liver, spleen, tracheobronchial lymph nodes, brain, and gross lesions. A summary of the most common pathology findings by group is shown in Table 7. Findings in the control group are very similar to the natural history studies. Group 1 (control) and Group 2 (levofloxacin-treated) are generally distinguishable, with differing patterns of pulmonary and hepatic inflammation, except for pleural fibrosis and periportal liver inflammation (Table 7).

Bacterial contamination with organisms other than *Y. pestis* was observed for 9 blood samples from animals that were still alive. The contaminated blood samples came from 4 levofloxacin-treated and 2 control animals. Contamination was also observed in some blood and tissue samples from terminal animals as well as the catheter tip. The bacterial contamination was not believed to be the result of a secondary infection but instead thought to be the result of technical errors (i.e. excessive moisture condensation on bacteria plates), human error (i.e. introduction of bacterial contaminants during sample processing) or possibly a biofilm localized to the catheter.

Table 7: Prominent Pathology Findings in Levofloxacin Treated and Control Groups (Study FY07-070)

	Group 1 Control		Group 2 Levofloxacin	
	Incidence (7 examined)	Average Severity[a]	Incidence (17 examined)	Average Severity[a]
Lung, inflammation, fibrinosuppurative and hemorrhagic with bacteria	7	3.8	0	0
Lung, inflammation, chronic, perivascular	0	0	15	1.3
Lung, inflammation, histiolymphocytic	0	0	13	1.3
Pleural fibrosis	3	0.8	8	0.9
Tracheobronchial lymph node edema	6	2.2	0	0
Tracheobronchial lymph node bacteria	7	3.5	0	0
Spleen, bacteria	2	0.8	0	0
Liver, inflammation, chronic (periportal)	5	0.7	9	0.6
Liver, inflammation, mixed (sinusoidal)	0	0	8	0.4
Brain, intravascular bacteria	4	0.9	0	0

[a] Lesions were graded subjectively by a single pathologist on a scale of 1 - 4: 1=minimal, 2=mild, 3=moderate, 4=marked

The efficacy of levofloxacin in treating pneumonic plague in AGMs was evaluated. Under the conditions of this study, levofloxacin administered intravenously for 10 days with 8 mg/kg followed by a 2 mg/kg dose 12 hours later resulted in 94% survival rate (16 of 17 animals) compared to a 0% survival rate in untreated control animals (a statistically significant difference, $p \leq 0.001$ by Fisher's Exact Test). This dosing regimen in AGMs achieved 53% of the human C_{max} and 25% of the AUC_{0-24} in humans. Fever in the treated survivors typically resolved in 3 to 4 days while bacteremia resolved before the next daily blood draw.

Multiple post-hoc sensitivity analyses were performed for the primary endpoint, the proportion of AGMs surviving. A stratified Fisher's exact test (FET), adjusting for the different cohorts, provided a p value of 0.001. If Cohort 3 was excluded because of questions concerning the challenge dose received, then the survival rates would be 0/5 for controls and 9/9 for levofloxacin-treated AGMs; unstratified and stratified FET p values would be <0.001 and 0.001, respectively. Excluding 4 levofloxacin AGMs for which bacteremia was not noted, the survival rates would be 0/7 for controls and 12/13 for levofloxacin-treated AGMs; unstratified and stratified FET p values would be <0.001 and 0.001, respectively.

4. CLINICAL/POST-MARKETING SAFETY

In FDA's Draft Guidance for Industry: Animal Models — Essential Elements to Address Efficacy Under the Animal Rule (January 2009), the body of available human safety data,

including data from the product's evaluation and use in other indications, is a critical component of any product's development plan and influences the benefit/risk considerations. As such, Janssen has referenced the previous findings of clinical and post-marketing safety for LEVAQUIN for the review of human safety data in these sNDAs.

LEVAQUIN was approved for use in the U.S. in 1996 for the treatment of a number of respiratory, urinary tract and skin, and soft tissue infections (see Section 2.1.3). Adverse reactions were assessed in 7537 patients from 29 pooled Phase 3 clinical trials. The most common adverse drug reactions (ADRs; based on incidence rates) were nausea (7%) followed by headache (6%), diarrhea (5%), insomnia (4%), dizziness (3%), and constipation (3%). The incidence rates of these common ADRs are similar for the 500 mg and 750 mg dosing regimens.

Post-marketing data indicate that the estimated exposure to LEVAQUIN is approximately 300 million treatment courses in the U.S. as of 31 March 2011. Review of spontaneous post-marketing reports has identified the following ADRs including: tendonitis, tendon rupture, exacerbation of myasthenia gravis, hypersensitivity reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic failure, pseudotumor cerebri, peripheral neuropathy, torsade de pointes, and QT prolongation. A detailed overview of the safety profile is provided in the USPI (see Attachment 2).

LEVAQUIN was also approved for the treatment of inhalational anthrax (post-exposure) by FDA in November 2004 (adults) and May 2008 (pediatric patients). The recommended dose regimen in adults and children weighing ≥50 kg and ≥6 months of age is 500 mg given once daily for 60 days. For children weighing <50 kg and ≥6 months of age, the recommended dosage regimen is 8 mg/kg twice a day (not to exceed 250 mg/dose) for 60 days. The approved dose regimen for inhalational anthrax in children is 46 days longer than the proposed dose regimen for pneumonic plague. Given the severity of infection and the relatively short treatment period for pneumonic plague, no unforeseen safety issues are expected.

Since the first approval in 1996, post-marketing surveillance of drug adverse events associated with the use of LEVAQUIN was initiated and evaluated on an ongoing basis. Post-marketing safety surveillance includes the systematic collection of adverse event reports from multiple sources including medical personnel, non-medical personnel, medical literature and regulatory agencies. Using these collected adverse events, safety professionals conduct real time and periodic medical assessments of single and aggregate reports to identify potential changes to the safety profile of the product. Safety data from post-marketing surveillance are described in the USPI (see Attachment 2). The safety profile of LEVAQUIN has been well characterized at dosage regimens in adults of 500 mg given once daily for up to 28 days and 750 mg given once daily for up to 14 days. The most recent Periodic Safety Update Report (PSUR) covering the time period from 01 October 2010 to 30 September 2011 was submitted to FDA on 21 November 2011 after the submission of the sNDAs. The data were consistent with the safety profile outlined in the USPI (see Attachment 2) and the favorable risk-benefit balance of levofloxacin remained unchanged.

4.1. Boxed Warnings/Class Labeling for Fluoroquinolones: Warnings and Precautions

WARNING: Fluoroquinolones, including LEVAQUIN, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Fluoroquinolones, including LEVAQUIN, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid LEVAQUIN in patients with a known history of myasthenia gravis. These warnings appear as BOXED WARNINGS in the USPI.

Other WARNINGS and PRECAUTIONS include:

- Hypersensitivity reactions, including anaphylactic reactions, anaphylactic shock, angioneurotic edema
- Other serious and sometimes fatal reactions; clinical manifestations may include one or more of the following:
    - fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
    - vasculitis; arthralgia; myalgia; serum sickness;
    - allergic pneumonitis;
    - interstitial nephritis; acute renal insufficiency or failure;
    - hepatitis; jaundice; acute hepatic necrosis or failure;
    - anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.
- Hepatotoxicity, including hepatic failure
- Central nervous system effects, including convulsions, pseudotumor cerebri
- *Clostridium difficile*-associated diarrhea
- Peripheral neuropathy
- Prolongation of the QT interval/ torsade de pointes
- Musculoskeletal disorders in pediatric patients
- Blood glucose disturbances
- Photosensitivity/phototoxicity
- Development of drug resistant bacteria

Further safety information, including information on Warnings and Precautions, is provided in the LEVAQUIN USPI in Attachment 2.

4.2. Clinical/Post-Marketing Safety Conclusions

LEVAQUIN has a well-defined safety profile at dosage regimens in adults of 500 mg given once daily for up to 28 days and 750 mg given once daily for up to 14 days. The proposed dosing recommendations for pneumonic plague (post-exposure) are for the same or lower doses and the same or shorter duration than the approved dosage regimens in adults for nosocomial pneumonia, community-acquired pneumonia, acute bacterial sinusitis, complicated skin and skin structure infections, chronic bacterial prostatitis and inhalational anthrax (post-exposure). The proposed pediatric dosage recommendation for plague (post-exposure) is also for the same dose but for shorter duration than the recommended pediatric dose for inhalational anthrax (post-exposure). Thus, the safety of LEVAQUIN (levofloxacin), as presented in the USPI, is predictable and well-characterized and meets the requirements for clinical safety assessment as defined in the Animal Rule.

5. CLINICAL EXPERIENCE IN PEDIATRIC PATIENTS

5.1. Efficacy and Safety in Pediatric Clinical Trials

LEVAQUIN is not indicated for pediatric patients (less than 18 years of age) for infections other than anthrax (post-exposure). It is generally accepted that fluoroquinolones should not be used in children, largely because these drugs have been shown to cause lesions in the cartilage of juvenile animals.[35] LEVAQUIN was evaluated in children with recurrent or persistent acute otitis media and in children with CAP. A subset of children from these clinical trials enrolled in a prospective, long-term surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendinopathy, gait abnormality). The incidence of musculoskeletal disorders during 60 days and 1 year following the first dose of the study drug was significantly higher in LEVAQUIN-treated children when compared to the non-fluoroquinolone-treated children.

Bacterial pneumonia is an important cause of morbidity and mortality in adults and children. LEVAQUIN's broad spectrum of activity includes the leading bacterial and atypical pneumonia pathogens. LEVAQUIN's efficacy and safety in the treatment of CAP in adults has been well-established. To assess the clinical efficacy and safety of LEVAQUIN compared with standard of care antibiotic therapy in the treatment of CAP in a pediatric population, 738 children aged 6 months to 16 years were enrolled in an open-label, multicenter, noninferiority trial.[6] Children with CAP were randomized 3:1 to receive LEVAQUIN or comparator antimicrobial therapy (children aged 0.5 to <5 years received amoxicillin/clavulanate or ceftriaxone; children ≥5 years received clarithromycin or ceftriaxone with clarithromycin or erythromycin lactobinate) for 10 days. For children >6 months to <5 years, the LEVAQUIN dose was 10 mg/kg BID (up to 500 mg/d) and for children >5 to 16 years, LEVAQUIN 10 mg/kg QD (up to 500 mg/d) was administered. The primary outcome was cure rates at the test-of-cure visit (10-17 days after completing treatment) as determined by symptoms, physical examination, and chest radiography. Five hundred thirty-nine subjects (405 LEVAQUIN -treated, 134 comparator-treated) were clinically evaluable at the test-of-cure visit. Clinical cure rates were 94.3% (382 of 405) in LEVAQUIN -treated children and 94.0% (126 of 134) in comparator-treated children. Cure rates

were also similar for LEVAQUIN and comparator within each age group (<5 years, 92.2% vs. 90.8%; ≥5 years, 96.5% vs. 97.1%; respectively, in the LEVAQUIN and comparator groups) and for children categorized as being at higher risk for severe disease. *Mycoplasma pneumoniae* was the most frequently identified cause of pneumonia (230 children). LEVAQUIN was as well tolerated as comparators, with similar type and incidence of adverse events (Table 8).

Table 8: Adverse Events Occurring in ≥5% of Subjects in Either Treatment Group in an Open-Label Study[a] of Pediatric Subjects with CAP Treated with LEVAQUIN Compared with Standard of Care

Adverse Events ≥ 5%	LEVAQUIN[b] (n=533)	Comparator[c] (n=179)
Diarrhea	7%	11%
Vomiting	6%	8%
Abdominal pain	5%	7%
Upper respiratory tract infection	5%	5%
Rhinitis	4%	6%
Bronchospasm	3%	6%
Fever	2%	6%

[a] Bradley JS, Arguedas A, Blumer JL, Sáez-Llorens X, Melkote R. Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia.: Pediatr Infect Dis J. 2007; 26(10): 865-7
[b] LEVAQUIN dose was 10 mg/kg BID (up to 500 mg/d) for children >6 months to <5 years, and 10 mg/kg QD (up to 500 mg/d) for children >5 to 16 years
[c] Comparator antimicrobial therapy (0.5 to <5 years: amoxicillin/clavulanate or ceftriaxone; ≥5 years: clarithromycin or ceftriaxone with clarithromycin or erythromycin lactobinate) for 10 days.

Two clinical trials have been conducted in 1855 children with recurrent or persistent acute otitis media. The objective of the first open-label, multicenter study[3] was to assess the efficacy and safety of LEVAQUIN treatment in the eradication of bacterial pathogens from the middle ear fluid (MEF) of children with, or at high risk for, persistent or recurrent otitis media. Two-hundred-five children (80% ≤2 years of age) were enrolled in the study; tympanocentesis was performed at study entry and selectively 3 to 5 days after starting LEVAQUIN (10 mg/kg BID for 10 days). One child did not have a confirmed diagnosis of acute otitis media and did not return for follow-up visits. Of the remaining 204 children, 94 (46%) had bilateral infection and 63 (31%) were receiving antimicrobials immediately before entry. One hundred five isolates of *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pyogenes* were recovered in pure or mixed cultures. All isolates were susceptible to LEVAQUIN. During-treatment bacterial eradication from MEF occurred in 88% (78 of 89) of bacteriologically evaluable patients, including 90% (65 of 72) of children ≤24 months of age. Bacteria initially isolated from MEF were eradicated in 31 of 37 (84%) children infected with *S. pneumoniae* and in 54 of 54 (100%) children infected with *H. influenzae*. Overall, clinical success rate after therapy was 94% for the total study population and 92% for the bacteriologically evaluable population. LEVAQUIN was well tolerated. Vomiting (4%) was the most common treatment-limiting adverse event.

The second study enrolled 1650 children in an evaluator-blinded, active-comparator, noninferiority, multicenter study.[43] Children (6 months to <5 years) were randomized 1:1 to receive LEVAQUIN (10 mg/kg BID) or amoxicillin/clavulanate (14:1; amoxicillin 45 mg/kg BID) for 10 days, with evaluations at 4 to 6 days of therapy (visit 2), 2 to 5 days after completing therapy (visit 3), and 10 to 17 days after the last dose (visit 4). The primary outcome was clinical cure at visit 3 based on resolution of clinical signs and symptoms of acute otitis media. Of the 1305 clinically evaluable children at visit 3, the clinical cure rates were 72.4% (456 of 630) in LEVAQUIN-treated and 69.9% (472 of 675) in amoxicillin/clavulanate-treated children. Cure rates were also similar for LEVAQUIN and comparator within each age group (≤24 months: 68.9% vs. 66.2%; >24 months: 76.9% vs. 75.1%; respectively). Cure rates at visit 4 were 74.9% and 73.8% in the LEVAQUIN and amoxicillin/clavulanate groups, respectively. The upper limits of the confidence intervals were less than the noninferiority margin of 10% indicating that LEVAQUIN treatment is noninferior to comparator treatment overall and in the subgroups of infants (6 months to ≤2 years) and children >2 to 5 years. No differences between treatment groups regarding the frequency or type of adverse events were apparent.[31]

5.2. Comparative Safety Profile of Musculoskeletal Disorders in LEVAQUIN-Treated Children and Non-fluoroquinolone-treated Children

A subset of children (1340 LEVAQUIN-treated and 893 non-fluoroquinolone-treated) in the 3 pediatric clinical trials of LEVAQUIN in the treatment of acute otitis media and CAP were enrolled in a prospective, long-term, surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendinopathy, gait abnormality).

Children treated with LEVAQUIN had a significantly higher incidence of musculoskeletal disorders when compared to the non-fluoroquinolone-treated children during 60 days (2.1% vs. 0.9%; P = 0.04) and 1 year (3.4% vs. 1.8%; P = 0.03) following the first dose of the study drug. Arthralgia was the most frequently-occurring musculoskeletal disorder in both treatment groups. Most of the musculoskeletal disorders in both groups involved multiple weight-bearing joints. Disorders were moderate in 8/46 (17%) children and mild in 35/46 (76%) of LEVAQUIN-treated children. The median time to resolution was 7 days for LEVAQUIN-treated children and 9 for non-fluoroquinolone-treated children. No child had a severe or serious disorder and all musculoskeletal disorders resolved without sequelae (see USPI; Attachment 2).[42] In contrast to the assessment at day 60 and 1 year, the incidence of musculoskeletal disorders at the 5-year follow-up were higher in the comparator group [3/83 (3.6%) children] compared with the LEVAQUIN group [3/124 (2.4%) children]. Independent of treatment assignment, there was no evidence of growth impairment.[31]

5.3. Clinical Pediatric Experience Conclusion

In 3 pediatric studies, LEVAQUIN was demonstrated to be effective in children with CAP and acute otitis media. Common adverse events were similar in LEVAQUIN-treated and non-fluoroquinolone antibiotic-treated children and the initial higher incidence of musculoskeletal disorders reversed as children were followed up to 5 years. Given the life-threatening nature of pneumonic plague, the benefit to use levofloxacin in children outweighs the risk.

6. SUMMARY OF BENEFITS AND RISKS

Because of ethical concerns and infeasibility, in vivo evaluation of the efficacy of levofloxacin in the treatment of pneumonic plague cannot be conducted directly in humans and must rely on the results of animal models. In accordance with 21 CFR 314.610, (i.e., the Animal Rule), FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of 21 CFR 314.610 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans.

As is the case for other agents from the fluoroquinolone class (e.g., ofloxacin, ciprofloxacin and moxifloxacin), several studies have shown that levofloxacin exhibits potent in vitro activity against *Y. pestis*. Data from an in vitro pharmacodynamic, hollow-fiber infection model conducted with *Y. pestis* also supports the potential efficacy of levofloxacin in plague treatment.[37] Further, there have not been any reports of clinical *Y. pestis* isolates resistant to fluoroquinolones. This is in contrast to reports that have documented resistance to antibacterials recommended for therapy and prophylaxis of *Y. pestis* infections (chloramphenicol, streptomycin, sulfonamides, tetracycline) as well as others including ampicillin, kanamycin, spectinomycin and minocycline.[23, 25]

In animal studies of plague disease, ofloxacin (a racemic mixture which consists of 50% levofloxacin) has been reported to be efficacious in both rodent[5,7 ,2,53] and primate[49] models of *Y. pestis* infection. In specific studies of levofloxacin, 2 separate studies (Studies RIID-YpEff-2006 and UTMB-YpEff-1-8) have reported efficacy in mouse models of primary pneumonic plague.[27, 48]

Studies conducted to characterize the natural history disease progression of pneumonic plague following aerosol exposure of AGMs to *Y. pestis* confirmed that the disease in AGMs shares many features with human clinical disease (Studies F03-09G, FY06-126, 617-G607610, and 875-G607610) (Attachment 1). Fever and bacteremia are the most prominent features during the course of disease in AGMs, and lung pathology is the most prominent feature in animals that succumb to disease, along with dissemination of bacteria to other tissues such as lymph nodes, spleen, liver and occasionally brain (meninges). The clinical presentations in AGMs are very similar to those in humans, including fever in 100% of cases (typically 3 days post-exposure in AGMs), the presence of *Yersinia pestis* in body fluids, elevated heart rate, elevated respiration rate late in the disease, pulmonary infiltrates (largely bilateral) on chest radiographs, and similar lung pathologies. The similarities observed between humans and AGMs in the clinical presentations of pneumonic plague indicate that the AGM pneumonic plague model is a satisfactory model of human pneumonic plague.

In a GLP efficacy study in the AGM plague model (Study FY07-070), levofloxacin administered intravenously for 10 days with 8 mg/kg followed by a 2 mg/kg dose 12 hours later resulted in a 94% survival rate (16 of 17 animals) compared to a 0% survival rate in untreated control animals (a statistically significant difference, $p \leq 0.001$ by Fisher's Exact Test). This dosing regimen in AGMs achieved 53% of the human C_{max} and 25% of the AUC_{0-24} in humans. Fever in the treated

survivors typically resolved in 3 to 4 days while bacteremia resolved before the next daily blood draw.

As outlined in the Guidance for Industry: Animal Models — Essential Elements to Address Efficacy Under the Animal Rule, there are 4 conditions that must be met in order for FDA to rely on the evidence from animal studies to provide substantial evidence of effectiveness. Corresponding to these 4 conditions (see Section 2.5.1), the sponsor has demonstrated that:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of *Y. pestis* and its prevention or substantial reduction by the product. The pathophysiology of plague in the AGM model and in humans has been well-characterized in both the natural history studies in AGMs and in the literature. Further, Study FY07-070 demonstrated a significant effect of levofloxacin treatment on mortality in the AGM plague model.
2. The effect of levofloxacin on plague due to *Y. pestis* has been demonstrated in the AGM model of plague, a well-characterized animal model for predicting the response in humans. In addition, levofloxacin has been demonstrated to be effective in 2 rodent models of plague.
3. The study endpoint in Study FY07-070 was enhancement of survival, which is clearly related to the desired benefit in humans.
4. The data or information on the pharmacokinetics and pharmacodynamics of levofloxacin allowed selection of an effective dose in humans.

Thus, the sponsor proposes that the data from the single Good Laboratory Practice (GLP) study conducted in AGMs and supporting information from the literature on the efficacy of levofloxacin in rodent models of plague infection provide the substantial evidence of effectiveness outlined in 21 CFR 314.610.

LEVAQUIN (levofloxacin) has been approved in the U.S. since 1996 for the treatment of a variety of specific infections. The estimated exposure to LEVAQUIN in the U.S. is approximately 300 million treatment courses as of 31 March 2011, and it has a well-defined and predictable safety profile at dosage regimens in adults of 500 mg given once daily for up to 28 days and 750 mg given once daily for up to 14 days. This safety profile supports the proposed indication for pneumonic plague (post-exposure), since the proposed dosage recommendations (see Section 2.1) are for the same or lower doses and the same or shorter duration than the approved dosage regimens in adults for nosocomial pneumonia, community-acquired pneumonia, acute bacterial sinusitis, complicated skin and skin structure infections, chronic bacterial prostatitis and inhalational anthrax (post-exposure). The proposed pediatric dosage recommendation for plague (post-exposure) is also for the same dose but for shorter duration than the recommended pediatric dose for inhalational anthrax (post-exposure). Given the severity of infection and the relatively short treatment period for pneumonic plague, no unforeseen safety issues are expected.

Y. pestis has several characteristics that make it a significant concern for use as a biological weapon; it can be found in many regions of the world, can be mass-produced, can be disseminated through direct aerosolization, can be spread through person-to-person contact and therefore has high potential for secondary spread of cases during an epidemic, has rapid onset of

lethal symptoms and has a very high fatality rate in the pneumonic form of the disease. All of these characteristics are key factors underlying its classification as a Category A Bioterrorism Agent in the U.S.[41] Should a terrorist attack involving the mass exposure of U.S. citizens to aerosolized *Y. pestis* occur, the size of a pneumonic plague outbreak would depend on several factors including the quantity of biological agent used, characteristics of the strain, environmental conditions, and methods of aerosolization.[30]

In a mass casualty setting, administration of parenteral antibiotic therapies would be impractical, if not impossible, due to logistics, shortages of supplies and trained personnel necessary to administer them. Therefore, an approved oral antibiotic therapy would be highly preferred in a scenario where large portions of the population were exposed to *Y. pestis*. In addition to being available in both oral and parenteral formulations, LEVAQUIN also offers other advantages for use in a mass casualty setting, such as availability of adequate supplies of drug, once daily dosing, high oral bioavailability, no food interactions, and overall good distribution and tissue penetration. Following its approval for anthrax (post-exposure), supplies of both oral and parenteral formulations of LEVAQUIN have been stockpiled by the CDC and the DOD. Levofloxacin has a relatively long shelf-life (up to 2 years) and products are available in sizes small enough to facilitate storage of large quantities which can also be readily shipped in the event of an emergency. The existing stockpiles of LEVAQUIN as well as generic formulations of levofloxacin would be able to meet demand in the event of a bioterrorism attack were LEVAQUIN also approved for pneumonic plague (post-exposure). For all the reasons cited above, LEVAQUIN could potentially save many lives of individuals exposed to *Y. pestis* in a bioterrorist attack.

Given the well-defined and predictable safety profile of LEVAQUIN and its suitability for use in a mass casualty setting, it appears clear that any potential risk of LEVAQUIN administration is outweighed by the benefits received for the indication pneumonic plague (post-exposure).

7. CONCLUSIONS

- The pathophysiological mechanism of the toxicity of *Y. pestis* in pneumonic plague is well understood, based on natural history studies conducted in AGMs and literature accounts of cases of untreated human plague from the pre-antibiotic era.
- Levofloxacin has been shown to be effective against *Y. pestis* in vitro, and in rodent models of plague.
- The AGM model of plague has been demonstrated to be a well-characterized model for predicting the effectiveness of antibiotic therapy for the treatment of human plague due to *Y. pestis*.
- The levofloxacin dosing regimen (8 mg/kg followed by a 2 mg/kg dose 12 hours later intravenously for 10 days) in AGMs achieved 53% of the human C_{max} and 25% of the AUC_{0-24} in humans.
- In a GLP efficacy study in the AGM plague model (Study FY07-070), levofloxacin administered intravenously at a dose of 8 mg/kg followed by a 2 mg/kg dose 12 hours later for 10 days resulted in a 94% survival rate (16 of 17 animals) compared to a 0% survival

rate in untreated control animals (a statistically significant difference, $p \leq 0.001$ by Fisher's Exact Test).

- Comparable favorable safety profile can be supported for plague indication as in other approved indications for both adult and pediatric use based on similar or lower dosing regimens and of longer treatment durations.
- Based on lethality of pneumonic plague and well characterized safety and tolerability, benefits of LEVAQUIN treatment of pneumonic plague would be expected to outweigh any potential risks .

The availability of an FDA-approved product with the proposed indication for pneumonic plague following exposure to *Y. pestis* would be expected to yield meaningful public health benefits in the event of a bioterrorism attack involving dissemination of *Y. pestis*. Janssen is appreciative of the Committee's review of LEVAQUIN for this purpose and looks forward to your input.

REFERENCES

1. Alsofrom DJ, Mettler FA, Mann JM. Radiologic manifestations of plague in New Mexico, 1975- 1980: A review of 42 proved cases. Radiology 1985; 139:561-5.
2. Andrews JM, Honeybourne D, Jevons G, Brenwald NP, Cunningham B and Wise R. Concentrations of levofloxacin (HR 355) in the respiratory tract following a single oral dose in patients undergoing fibre-optic bronchoscopy. J Antimicrob Chemother 1997; 40:573–7.
3. Arguedas A, Dagan R, Pichichero M, Leibovitz E, Blumer J, McNeeley DF, Melkote R, Noel GJ. An open-label, double tympanocentesis study of levofloxacin therapy in children with, or at high risk for, recurrent or persistent acute otitis media. Pediatr Infect Dis J. 2006; 25(12):1102-9.
4. Benner GE, GP Andrews, et al. Immune response to *Yersinia* outer proteins and other *Yersinia pestis* antigens after experimental plague infection in mice. Infect. Immun. 1999; 67:1922-1928.
5. Bonacorsi SP, Scavizzi MR, Guiyoule A, Amouroux JH and Carniel E. Assessment of a fluoroquinolone, three β-lactams, two aminoglycosides, and a cycline in treatment of murine *Yersinia pestis* infection. Antimicrob Agents Chemother. 1994; 38(3): 481-6.
6. Bradley JS, Arguedas A, Blumer JL, Sáez-Llorens X, Melkote R. Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia. Pediatr Infect Dis J. 2007; 26(10): 865-7.
7. Byrne WR, SL Welkos, et al. Antibiotic treatment of experimental pneumonic plague in mice. Antimicrob. Agents Chemother. 1998; 42: 675-681.
8. Centers for Disease Control and Prevention. Fatal Human Plague. Morb Mortal Wkly Rep. 1997; 43:380-382.
9. Centers for Disease Control. Human Plague- Four States, 2006. MMWR 2006; 55(34):940-3.
10. Chien S, Wells T G, Blumer JL, Kearns GL, Bradley JS. Bocchini JA. Jr., Natarajan J, Maldonado S, and Noel GJ, Levofloxacin Pharmacokinetics in Children. J Clin Pharmacol 2005; 45:153-160.
11. Chun JWH [a]. Clinical features. In Wu Lien-Teh, Chun JWH, Pollitzer R, and Wu CY. Plague: A manual for medical and public health workers. Shanghai Station, China: Weishengshu National Quarantine Service; 1936:309-333.
12. Chun JWH [b]. Therapy and personal prophylaxis. In Wu Lien-Teh, Chun JWH, Pollitzer R, and Wu CY. Plague: A manual for medical and public health workers. Shanghai Station, China: Weishengshu National Quarantine Service; 1936:334-53.
13. CLSI. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria: approved guidelines, 2nd edition. Vol. M45-A2. 2010. Clinical and Laboratory Standards Institute.
14. CLSI. Performance standards for antimicrobial susceptibility testing: 21st informational supplement. Vol. M100-S21. 2011. Clinical and Laboratory Standards Institute.
15. Davis KJ, Fritz DL , Pitt ML, Welkos SL, Worsham PL, et al. Pathology of experimental pneumonic plague produced by fraction 1-positive and fraction 1-negative *Yersinia pestis* in African green monkeys (*Cercopithecus aethiops*). Arch Pathol Lab Med. 1996; 120:156–163.
16. Dempster AM, Latriano L, Tolman E, McKenzie BE, Ferriaolo BL, Peterson PA. Pharmacology, Toxicology and Absorption, Distribution, Metabolism, and Excretion (ADME) of Levofloxacin. (Refer to Section IV/Subsection H, 375-389). Document ID No.: 370190:3; 07 September 1995. Submitted in NDA 20-634, approved on 20 December 1996.
17. Dennis DT, Mead PS. Yersinia species, including plague. In Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 7th ed. Philadelphia, PA: Churchill Livingstone; 2009:2943-53.
18. Doll JM, PS Zeitz, P Ettestad et al. Cat-transmitted fatal pneumonic plague in a person who traveled from Colorado to Arizona. Am J Trop Med Hyg 1994; 51(1):109-14.
19. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin. Pharmacokinet. 1997; 32 (2): 101-119.

20. Frean JA, Arntzen L, Capper T, Bryskier A, and Klugman KP. *In Vitro* Activities of 14 Antibacterials against 100 Human Isolates of *Yersinia pestis* from a Southern African Plague Focus. Antimicrob Agents and Chemother. 1996; 40(11): 2646-47.

21. Frean J, Klugman KP, et al. Susceptibility of Yersinia pestis to novel and conventional antimicrobial agents. J. Antimicrob. Chemother. 2003; 52: 294-296.

22. Friedlander AM, Welkos SL, Worsham PL, Andrews GP, Heath DG, et al.. Relationship between virulence and immunity as revealed in recent studies of the F1 capsule of *Yersinia pestis*. Clin. Infect. Dis. 1995; 21(Suppl. 2):S178–S181.

23. Galimand, M, Guiyoule A., et al. Multidrug resistance in *Yersinia pestis* mediated by a transferable plasmid. New Engl. J. Med. 1997; 337: 677-681.

24. Gotfried MH, Danziger LH, Rodvold KA. Steady-State Plasma and Intrapulmonary Concentrations of Levofloxacin and Ciprofloxacin in Healthy Adult Subjects. Chest. 2001: 119 (4): 1114-1122.

25. Guiyoule, A., Gerbaud G., et al. Transferable plasmid-mediated resistance to streptomycin in clinical isolate of Yersinia pestis. Emerg. Infect. Dis. 2001; 7: 43-48.

26. Health aspects of chemical and biological weapons, 1st edition. Geneva, Switzerland: World Health Organization; 1970.

27. Heine HS, Louie A, Sorgel F, Bassett J, Miller L, Sullivan LJ, Kinzig-Schippers M, Drusano G L. Comparison of 2 antibacterials that inhibit protein synthesis for the treatment of infection with *Yersinia pestis* delivered by aerosol in a mouse model of pneumonic plague. J. Infect. Dis. 2007; 196(5):782-7.

28. Hemeryk A, Mamidi R, Bottacini D, Macpherson M, Kao M, and Kelley M. Pharmacokinetics, metabolism, excretion and plasma protein binding of ^{14}C-levofloxacin after a single oral administration in the Rhesus monkey. Xenobiotica 2006; 36:597-613.

29. Hernandez E, Girardet M., et al. Antibiotic susceptibilities of 94 isolates of Yersinia pestis to 24 antimicrobial agents. J. Antimicrob. Chemother. 2003; 52: 1029-1031.

30. Inglesby TV, Dennis DT, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Friedlander AM, Hauer J, Koerner JF, Layton M, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Schoch-Spana M, Tonat K. Plague as a Biological Weapon: Medical and Public Health Management. JAMA 2000; 283(17): 2281-90.

31. Johnson & Johnson Pharmaceutical Research & Development, L.L.C. A Long-term Study of the Incidence of Musculoskeletal Disorders in Children Who Have Received Levofloxacin or a Standard Non-fluoroquinolone Therapy for Acute Bacterial Infection. ClinicalTrials.gov Identifier: NCT00210639 http://clinicaltrials.gov/ct2/show/NCT00210639 Last accessed February 27, 2012

32. Kao LM, Bush K, Barnewall R, Estep J, Thalacker FW, Olson, et al. Pharmacokinetic consideration and efficacy of levofloxacin in an inhalation anthrax (postexposure) rhesus monkey model. Antimicrob Agents Chemother. 2006; 50(11):3535-42.

33. Layton RC, W Mega, et al. Levofloxacin cures experimental pneumonic plague in African green monkeys. PLoS Negl. Trop. Dis. 2011; 5: e959.

34. Lee LJ, Sha X, Gorfried MH, Howard JR, Dix RK, Fish DN. Penetration of levofloxacin into lung tissue after oral administration to subjects undergoing lung biopsy or lobectomy. Pharmacotherapy. 1998 18(1):35-41.

35. Li, F., Nandy P., Chien S., Noel G. J., and Tornoe C. W., Pharmacometrics-Based Dose Selection of Levofloxacin as a Treatment for Postexposure Inhalational Anthrax in Children. Antimicrobial Agents and Chemotherapy. 2010; 54(1): 375–379.

36. Lonsway DR, Urich SK , et al. Comparison of etest method with reference broth microdilution method for antimicrobial susceptibility testing of Yersinia pestis. J. Clin. Microbiol. 2011; 49: 1956-1960.

37. Louie A, Deziel MR, Liu W, Drusano GL. Impact of Resistance Selection and Mutant growth Fitness on the Relative Efficacies of Streptomycin and Levofloxacin for Plague Therapy. Antimicrob Agents Chemother. 2007; 51(8): 2661-67.

38. Louie A, Heine HS, et al. Use of an in vitro pharmacodynamic model to derive a moxifloxacin regimen that optimizes kill of Yersinia pestis and prevents emergence of resistance. Antimicrob. Agents Chemother. 2011; 55: 822-830.

39. McGovern TW, Friedlander AM. Plague. In: Zajtchuk R, Bellamy RF, eds. Medical aspects of chemical and biological warfare. Falls Church, VA: Office of the Surgeon General, United States Army; 1997:479-502.

40. Meyer KF, Smith G, Foster L, Brookman M, Sung M. Live, attenuated Yersinia pestis vaccine: virulent in nonhuman primates, harmless to guinea pigs. J. Infect. Dis. 1974; 129(Suppl.): S85-S120.

41. National Institute of Allergy and Infectious Disease (NIAID) Biodefense web page (2010) accessible via: http://www.niaid.nih.gov/topics/biodefenserelated/biodefense/research/pages/cata.aspx.

42. Noel GJ, Bradley JS, Kauffman RE, Duffy CM, Gerbino PG, Arguedas A, Bagchi P, Balis DA, Blumer JL. Comparative Safety Profile of Levofloxacin in 2523 Children With a Focus on Four Specific Musculoskeletal Disorders.: Pediatr Infect Dis J 2007; 26: 879–891.

43. Noel GJ, Blumer JL, Pichichero ME, Hedrick JA, Schwartz RH, Balis DA, Melkote R, Bagchi P, Arguedas A. A randomized comparative study of levofloxacin versus amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media.: Pediatr Infect Dis J. 2008; 27(6):483-9.

44. Opulski et al. Pneumonic plague—Arizona, 1992. JAMA 1992; 268:2146 -2147.

45. Osborn BL. Dose Justification Report: Use of levofloxacin to treat plague in African Green monkeys. National Institute of Allergy and Infectious Disease, Dose Justification Report. 09 June 2010.

46. Osterholm MT, Schwartz J. Living terrors: what America needs to know to survive the coming bioterrorist catastrophe. New York: Delacorte Press: 2000

47. Perry RD, Fetherstone JD. *Yersinia pestis* – etiologic agent of plague. Clin Microbiol Rev. 1997; 10:35-66.

48. Peterson JW, Moen ST, Healy D, Pawlik JE, Taormina J, Hardcastle J, Thomas JM, Lawrence WS, Ponce C, Chatuev BM, Gnade BT, Foltz SM, Agar SL, Sha J, Klimpel GR, Kirtley ML, Eaves-Pyles T, Chopra AK. Protection Afforded by Fluoroquinolones in Animal Models of Respiratory Infections with *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularensis*. The Open Microbiology Journal 2010; 4: 34-46.

49. Romanov VE, Evstigneev VI, Vasil'ev NT, Shabalin BA, Paramonov VE. Evaluation of the effectiveness of antibacterial substances in treating an experimental form of bubonic plague in monkeys. Antibiot Khimioter. 2001; 46(8): 6-8.

50. Russell P, Eley SM, et al. Efficacy of doxycycline and ciprofloxacin against experimental Yersinia pestis infection. J. Antimicrob. Chemother. 1998; 41: 301-305.

51. Ryzhko IV, Shcherbaniuk AI, et al. Possibility of appearance of virulent antigen-modified mutants (Fra-, Fra-Tox-) of plague bacteria resistant to rifampicin and quinolones. Antibiot. Khimioter. 2003; 48: 19-23.

52. Ryzhko IV, Tsuraeva RI, et al. Efficacy of levofloxacin, lomefloxacin and moxifloxacin vs. Other fluoroquinolones in experimental plague due to F1+ and F1- strains of Yersinia pestis in albino mice. Antibiot. Khimioter. 2009; 54: 37-40.

53. Samokhodkina ED, Shcherbaniuk AI, Ryzhko IV, Tsuraeva RI, Skalyga, EIu. Ofloxacin efficacy in the prophylaxis and treatment of experimental plague due to antigen complete and defective strains of the pathogen. Antibiot Khimioter. 2002; 47(3): 26-9.

54. Slack P. The black death past and present. Trans R Soci Trop Med Hyg. 1989; 83: 461-463.

55. Smith MD, Vinh DX, et al. In vitro antimicrobial susceptibilities of strains of Yersinia pestis. Antimicrob. Agents Chemother. 1995; 39: 2153-2154.

56. Ulrich SK, Chalcraft L, et al. Lack of antimicrobial resistance in Yersinia pestis isolates from 17 countries in the Americas, Africa, and Asia. Antimicrob. Agents Chemother. 2012; 56:555-558.

57. Von Baum H., Bottcher S, Hoffmann H, and Sonntag HG. Tissue penetration of a single dose of levofloxacin intravenously for antibiotic prophylaxis in lung surgery. J Antimicrob Chemother 2001; 47:719–30.

58. Werner SB, Weidmer CE, Nelson BC, Nygaard GS, Goethals RM, Poland JD. Primary plague pneumonia contracted from a domestic cat at South Lake Tahoe, Calif. J Am Med Assoc. 1984; 251(7):929-31.

59. Wong D, Wild MA, Walburger MA, Higgins CL, Callahan M, Czarnecki LA, et al. Primary pneumonic plague contracted from a mountain lion carcass. Clin Infect Dis 2009; 49:e33-38.

60. Wong, J. D., J. R. Barash, et al. Susceptibilities of Yersinia pestis strains to 12 antimicrobial agents. Antimicrob. Agents Chemother. 2000; 44: 1995-1996.

61. Wu Lien-Teh. A Treatise on Pneumonic Plague. Geneva, Switzerland: League of Nations. III. Health Organization; 1926:241-95.

Attachment 1

Attachment 1

Natural History of Pneumonic Plague in the African Green Monkey

The following text describing the natural history of pneumonic plague in AGMs and comparing human and AGM natural courses of plague is taken from documentation provided by NIAID to Janssen on 22 February 2012. At the time of preparation of this briefing document, Janssen understood that this information was to be included in the briefing document provided to the Advisory Committee by the FDA. Nonetheless, Janssen has included the information as an Attachment to this briefing document for completeness and ease of review.

1. Natural History of Pneumonic Plague in African Green Monkeys

The first detailed natural history study of pneumonic plague in AGMs was performed at USAMRIID in June, 2003 (F03-09G). Results from this study allowed the subsequent testing of antibiotics in a treatment setting at USAMRIID. Subsequent efforts required transfer of the pneumonic plague model to additional laboratories. Additional natural history studies were carried out at LRRI (FY06-126 in April 2007) and BBRC (617-G607610 in July 2007, and 875-G607610 in January 2009). These were the first studies at each of these laboratories to assess disease progression in the AGM exposed to inhaled *Y. pestis*; therefore they were not intended to be conducted in compliance with GLP requirements. Good documentation practices and good scientific practices were followed.

1.1 Natural History Study of Pneumonic Plague in the African Green Monkey (Study No.F03-09G-Phase-1)

The objective of this study (F03-09G) was to evaluate clinical signs of pneumonic plague disease after aerosol challenge of AGMs, such that clinical signs could be used in future studies conducted in the animal model to assess the treatment efficacy of therapeutic agents. This study was conducted in two phases, and only the first phase is summarized here, as the second phase tested an antibiotic. Six healthy, experimentally naïve, adult AGMs (3 male, 3 female) weighing 3.5 to 6.0 kg were placed on study. Prior to challenge, the animals had telemetry devices implanted, as well as vascular access ports for blood sampling. Eighty hours of baseline telemetry data were collected, with average readings every thirty minutes.

On the day of challenge, AGMs were anesthetized and minute volume was measured by whole-body plethysmography. Animals were then immediately exposed to the *Y. pestis* aerosol in a head-only chamber, with a target dose of 100 ± 50 LD50 equivalents. The duration of each aerosol exposure is directly related to the animal's minute volume to achieve the target challenge dose. Each animal's actual challenge dose was verified retrospectively by collecting the aerosol during the challenge in an all glass impinger and quantifying organisms by plating dilutions.

Post-challenge, blood was drawn each day for microbiology, hematology and clinical chemistry. Clinical signs were documented twice daily and telemetry recording resumed every 30 minutes. When clinical signs such as fever (>1.5°C above baseline for 2 hours) or increased respiration (assessed manually) indicated disease, animals were anesthetized for a chest radiograph and blood drawn for microbiology, hematology and clinical chemistry; timing was 80 or 83 hours post-challenge. Clinical signs were also recorded more frequently for animals showing signs of disease (euthanasia scores); four areas were scored (activity, behavior, stimuli response and breathing; 5 points each) with a possible score of 20 for a normal animal and a score ≤5

triggering euthanasia. Microbiology during the post-challenge period was measured qualitatively by inoculating a BacTec™ PedsPlus™ culture bottle with 0.5 mL of blood and placing it in the BacTec™ instrument. Animals that met the pre-specified euthanasia criteria were anesthetized for a final radiograph prior to euthanasia. All animals that were found dead or euthanized were necropsied and gross and microscopic observations were recorded. Blood was drawn at euthanasia/necropsy for quantitative microbiology, by plating dilutions on blood agar.

Animals received between 9 and 57 LD50 equivalents (Table 1) with a mean dose of 25 ± 17 LD50 equivalents; four of the animals succumbed to disease, and those animals received more than 20 LD50 equivalents. The two animals that survived the challenge received 9 or 12 LD50 equivalents and never showed clinical signs or became bacteremic. These two surviving animals developed titers to the F1 and V antigens of *Y. pestis* and were therefore considered to have been exposed to the bacteria. One animal (V113) was qualitatively bacteremic at 48 hours, and all four animals that became bacteremic were positive by 72 hours and remained positive until death. At approximately 72 hours, animals started to demonstrate a fever (body temperature increase of >1.5°C over baseline) by telemetry. Fever was the first clinical sign of disease and retrospectively correlated very well with bacteremia. Once fever was noted, body temperature did not return to normal until falling rapidly just prior to death/euthanasia. The two survivors, while unexpected, reinforced the correlation between fever and disease, as those animals maintained a diurnal temperature pattern without a fever and never became bacteremic. Two animals showing signs of severe disease were euthanized while two additional animals succumbed after anesthesia though before euthanasia could be completed (see table note, Table 1). Respiratory rates increased only slightly at the time of fever and more dramatically as animals approached death/euthanasia. Clinical scores decreased only slightly at the time of fever in three animals (V627, V514, V113) and more dramatically in all animals as they approached death/euthanasia. Clinical scores and respiratory rates were normal and relatively unchanged in survivors over the course of the study. The number of animals that succumbed to disease in this study is small, and therefore, there were no significant differences between the sexes on time to death or terminal bacteremia levels, nor on development of disease. There were different profiles of white blood cells between males and females that developed disease, with males showing a terminal increase in their total white blood cells and females showing a terminal decrease. The significance of this observation is not understood and requires further exploration.

A complete gross necropsy was performed on all animals that succumbed to disease and all findings were recorded. The following tissues were collected at necropsy and fixed in 10% neutral buffered formalin: nares and lip, skin with mammary gland, submandibular salivary gland, mandibular lymph node, axillary lymph node, inguinal lymph node, mesenteric lymph node, brachial plexus, quadriceps muscle with sciatic nerve, heart, stomach (fundus and pyloris), duodenum, jejunum, ileum, cecum, proximal and distal colon, liver, gallbladder, spleen, pancreas, kidneys, adrenal glands, urinary bladder, prostate or uterus, gonads, eyes, pituitary gland, brain, femoral bone marrow, tongue, larynx, thyroid, parathyroid glands, trachea, esophagus, mediastinum, and lungs. Gross and microscopic necropsy findings for the four animals that succumbed are summarized in Table 2 and Table 3.

Table 1 F03-09G-Phase-1 Natural History: Challenge Dose, Survival, Fever, Bacteremia Observations

Animal ID	Sex	Challenge Dose, LD_{50} equivalents	1st Bacteremia, hours	Time to Fever, hours[a]	Respiratory Rate at 99 hours	Terminal Respiratory Rate	Outcome[b]	Time to Death, hours	Lowest Clinical Score	Terminal Bacteremia, CFU/mL
V627	M	57	72	72	80	140	EU	111.5	9	8×10^7
V514	F	30	72	72	88	146	EU	111	5	3×10^6
V569	M	23	72	67.5	128	128	D[c]	99.5	12	9×10^8
V113	F	21	48	74	72	168	D[c]	125	5	1×10^8
V605	M	9	--	--	36	--	S	--	19	--
V521	F	12	--	--	32	--	S	--	17	--

[a] Fever was defined as ≥ 1.5°C body temperature increase over baseline. Body temperature was monitored every 30 minutes via implanted telemetry devices.

[b] EU = euthanized; D = died; S = survived

[c] Animal met euthanasia criteria and died before it could be euthanized; see p. 197 or p. 201 of NIAID-Yp-NatHis-Path-2011

Table 2 F03-09G-Phase-1 Natural History: Prominent Gross Lesions

Animal ID	Sex	Red/purple foci in lungs	Fluid in trachea or bronchi	Mediastinal edema	Pleural effusion	Tracheobronchial lymphadenopathy
V627	M	+++[a]	+++	+/++	15-20 mL	++
V514	F	++	+++	+	neg	+
V569	M	++/+++	+++	++	30 mL	++
V113	F	+++	++	++	10-15 mL	++

[a] Severity: +++ = marked; ++ = moderate; + = mild; neg = not observed.

Table 3 F03-09G-Phase-1 Natural History: Microscopic Findings

Animal ID	Sex	Lungs	Mediastinal lymph nodes, inflammation and/or edema	Bronchial lymph nodes, inflammation and/or edema	Mediastinal connective tissue[b]
V627	M	++[a]	++	++	++
V514	F	+++	++	++	neg
V569	M	+++	+++	+	neg
V113	F	+++	++	++	++

[a] Severity: +++ = marked; ++ = moderate; + = mild; neg = not observed

[b] Findings included one or more of the following: edema, inflammation, hemorrhage.

The objective of the non-GLP F03-09G study was achieved in that clinical signs were monitored, recorded and described such that they could be used in determining the clinical assessments of relevance to the animal model as well as establishing clinical parameter criteria to use for euthanasia criteria in subsequent antibiotic efficacy studies. Among the six animals on Phase 1 of the study, there was a strong correlation between fever, bacteremia and non-survival.

1.2 Natural History Study of Inhalational Plague *Y. pestis* Strain CO92 in Adult Telemetered African Green Monkeys (Study No. FY06-126)

The objective of this study (FY06-126) was to confirm the natural history and lethality of aerosolized *Y. pestis* in the AGM at an additional site, LRRI. This study was the first *Y. pestis* aerosol challenge in AGMs performed at LRRI and therefore it was not intended to be compliant with GLP requirements. Good documentation and scientific practices were followed. Ten healthy, experimentally naïve, adult AGMs (5 male, 5 female) weighing 3 to 6 kg were placed on study. Prior to challenge, the animals had telemetry devices implanted, as well as vascular access ports (Broviac catheters) for blood sampling. Baseline telemetry data were collected, with average readings every five minutes. Arterial blood gas, clinical chemistry, hematology, coagulation and *Y. pestis* microbiology were also assessed in the baseline period.

The challenge material was prepared by streaking slants of TBAB with yeast extract with *Y. pestis* CO92 and incubating at 28°C for 48 to 72 hours. Growth was collected with 1% peptone using sterile swabs, pooled and vortexed. Optical density measurements determined the concentration of organisms, which were then diluted to the appropriate concentration for the target challenge dose.

On the day of challenge, AGMs were anesthetized and a baseline chest radiograph taken prior to challenge. Animals were then exposed to the *Y. pestis* aerosol in a head-only chamber in a Class III biosafety cabinet, with a target dose of 100 LD50 equivalents. Minute volume was measured by whole-body plethysmography in real time during the challenge. The duration of each aerosol

exposure is directly related to the animal's minute volume to achieve the target challenge dose. Each animal's actual challenge dose was verified retrospectively by collecting the aerosol during the challenge in an all glass impinger and quantifying organisms by plating dilutions. Challenges were performed on two separate days three weeks apart, with five animals challenged each day.

Post-challenge, blood was drawn each day for quantitative bacteriology, hematology, clinical chemistry, arterial blood gas, and coagulation indices. Clinical signs were documented twice daily and telemetry recording continued every 5 minutes. Animals were infused with saline every twelve hours beginning one day after challenge, in order to establish procedures for subsequent efficacy studies; procedures for catheter care were refined in the second challenge cohort; these infusions are unique to this natural history study. When increased respiration was noted by telemetry, animals were anesthetized for another chest radiograph; eight of the animals had chest radiographs on Day 0, Day 3 and Day 4, while two animals only had Day 0 and Day 3 (X790) or Day 0 and Day 4 (X789). Microbiology during the post-challenge period was measured quantitatively by plating of serial dilutions on tryptic soy agar (TSA) plates. Animals that were judged to be euthanized were first anesthetized for a chest radiograph and terminal blood was drawn for arterial blood gas, clinical chemistry, hematology, quantitative bacteriology and coagulation indices, prior to euthanasia. A complete gross necropsy was performed on all animals and all findings were recorded. Tissues taken at necropsy for terminal pathogen load were lung (lesion and non-lesion tissue), liver, spleen and tracheobronchial lymph nodes. Brain was collected for histopathology only.

Animals received between 44 and 255 LD50 equivalents with a mean dose of 135 ± 68 LD50 equivalents. All study animals became ill. Three animals died naturally and 7 were euthanized in a moribund condition (Table 4). The average challenge dose and standard deviation for the first challenge day was 190 ± 41 LD50 equivalents and for the second day was 79 ± 33 LD50 equivalents. All ten animals became bacteremic: three on Day 2 (all female), five on Day 3 (3 male, 2 female), and two at the time of death, Day 4 (both male). The animals that became bacteremic earliest demonstrated the highest levels of bacteremia and tended to be female (lower body weight). Females also tended to demonstrate higher numbers of bacteria in spleen and liver at necropsy. Fever was defined as a body temperature above 39°C for 2 hours, which correlated well with a 2°C increase over baseline body temperature, and was determined based on the data obtained in this study, and not defined prospectively.

The following tissues were collected at necropsy for terminal pathogen load: lung (lesion and non-lesion tissue), liver, spleen and tracheobronchial lymph nodes. The brain was also collected and fixed in 10% neutral buffered formalin for histopathology only. All animals on study had gross and microscopic lesions consistent with pneumonic plague (Table 5).

Bacterial contamination of blood samples taken via the Broviac catheter from live animals challenged on the first challenge day was problematic. Microbial characterization tests (coagulase and catalase) indicated that the contaminant was most likely a non-pathogenic Staphylococcus spp., presumably the normal flora microbe S. epidermidis. Blood samples drawn

from the femoral artery and tissue samples at necropsy were not contaminated which suggested that the staph contaminant may have come from a biofilm established on the Broviac catheter. A different Broviac catheter more suitable for sterile blood draws was used for animals challenged on the second challenge day and contamination was not an issue.

Table 4 FY06-126 Natural History: Challenge Dose, Survival, Fever and Bacteremia Observations

Animal ID	Sex	Challenge Dose, LD_{50} equivalents	1st Bacteremia, day	Time to Fever, hours[a]	Outcome[b]	Time to Death, hours[c]	Last Bacteremia, CFU/mL
X756†	M	255	4*	68	EU	95	1.7×10^2
X666†	F	206	3	75	EU	96	9.3×10^2
X538†	M	167	3	74	EU	93	2.1×10^2
X532†	M	163	3	87	EU	95	6.6×10^2
X705†	F	160	2	52	D	86	1.4×10^5◇
X789	F	129	3	74	D	99	$>2.0 \times 10^5$
X784	M	91	3	62	EU	100	1.3×10^3
X775	M	74	4*	79	EU	102	5.4×10^2
X774	F	58	2	52	EU	92	$>2.0 \times 10^6$
X790	F	44	2	52	D	71	$>2.0 \times 10^6$

† animals challenged on first challenge day

* first bacteremia was the terminal sample

◇ terminal sample not available; Day 3 result shown here

[a] Body temperature of 39°C for two consecutive hours was defined as the onset of fever

[b] EU = euthanized; D = died

[c] time to death as determined by telemetry data

Table 5 FY06-126 Natural History: Summary of Prominent Microscopic Findings

Animal ID	Lung inflammation	Pleural fibrosis	Tracheobronchial lymph node edema	Tracheobronchial lymph node bacteria	Spleen, bacteria	Liver, hydropic change	Brain
X756	+++[a]	-	+++	++++	-	++	U[b]
X666	+++	-	-	-	-	++++	U
X538	+++	-	-	+	-	+	U
X532	+++	+++	-	++	-	+++	U
X705	+++	-	+++	++++	+++		U
X789	++	++	+++	++	++++	+++	U
X784	+++	+++	-	++	-	++	U
X775	+++	-	-	+	-	+++	U
X774	+++	-	+++	++++	+++	-	U
X790	+++	+++	+++	+++	+++	-	U

[a] Severity: ++++ = marked; +++ = moderate; ++ = mild; + = minimal; - = finding not present or observed

[b] U = unremarkable organ/tissue

The study confirmed the progression of pneumonic plague in the AGM following aerosol exposure at LRRI. Fever and bacteremia were confirmed as consistent markers of disease for testing of antibiotic efficacy. Terminal bacteremia levels were somewhat lower than those seen in other studies, though the significance of this observation is unknown.

1.3 Natural Course of Untreated Pneumonic Plague in African Green Monkeys (Study No. 617-G607610)

The objective of this study (617-G607610) was the characterization of pneumonic plague disease through clinical observations, blood analyses and telemetric monitoring of physiological parameters of AGMs infected with aerosolized *Y. pestis*. This study was also intended to confirm the course of disease seen in previous studies, and to establish this model in another laboratory. The assessments in this protocol were designed to determine the timing of therapy in future efficacy studies. Ten experimentally naïve, healthy, adult AGMs (3 male, 7 female) weighing 3.3 to 4.7 kg were placed on study. Prior to challenge, the animals had telemetry devices implanted, and baseline telemetry data were collected, with average readings obtained every 15 minutes for at least seven days. Clinical observations were recorded daily. Clinical chemistry and hematology were also assessed prior to challenge, on Day 0. A memory B-cell assay was also performed to ensure that animals were naïve for exposure to *Yersinia* antigens; some very low values were observed that were considered background and therefore no animals were excluded from study.

The challenge material was prepared by first streaking *Y. pestis* CO92 on Congo red agar and heart infusion agar for isolation. After incubation at 26 ± 2°C for 66 hours, an isolated colony positive for the pigmentation locus in *Y. pestis* (Pgm+) was selected from the Congo red agar plate and used to inoculate HIB without $CaCl_2$ and incubated in a shaker incubator until reaching a target concentration of ~$2x10^9$ CFU/mL, measured by optical density at 600 nm. The bacteria were centrifuged, washed and resuspended in BSGT (buffered saline with 0.01% gelatin and 9.7% trehalose) at the target concentration for aerosolization.

On the day of challenge, AGMs were anesthetized and then exposed to the *Y. pestis* aerosol in a head-only chamber in a Class III biosafety cabinet, with a target dose of 100 LD_{50} equivalents. Minute volume was measured by whole-body plethysmography in real time during the challenge. Each animal's actual challenge dose was verified retrospectively by collecting the aerosol during the challenge in an all glass impinger and quantifying organisms by plating serial dilutions. All animal challenges were performed on a single day.

After challenge, clinical observations were recorded twice daily along with continuous telemetry monitoring. Blood was obtained daily for bacteremia, hematology and clinical chemistry. Bacteremia was determined by serial dilution and plating on TSA for quantitation. Samples were also streaked directly on Congo red agar, for qualitative assessment of colony morphology and pigmentation consistent with *Y. pestis*. Terminal blood samples were assessed qualitatively for *Y. pestis* bacteria.

Actual challenge doses ranged from 106 to 1150 LD_{50} equivalents with a mean of 613 ± 386 LD_{50} equivalents (Table 6). The spray factor, or the ratio between the aerosol concentration and the nebulizer concentration, varied by a log on this study. The starting nebulizer concentration also varied by more than a log, and accounts for a significant amount of the animal to animal variability in challenge dose. Subsequent studies investigated the aerosolization efficiency to bring it under tighter control and are not the subject of this summary. This study is being included here in support of the general disease pathogenesis.

Table 6 617-G607610 Natural History: Challenge Dose, Survival, Fever and Bacteremia Observations

Animal ID	Sex	Challenge Dose, LD_{50} equivalents	1st Bacteremia, day	Time to Fever, hours[a]	Outcome[b]	Time to Death, hours[c]	Last Bacteremia, CFU/mL[d]	Terminal Blood Culture Result[b]
X396	M	1150	2	41.2	D	61.6	$6.57x10^5$	pgm^+, C
X106	M	1094	2	38.8	D	85.8	$7.70x10^6$	pgm^+
X515	F	1024	2	36.6	D	68.9	$5.97x10^4$	pgm^+, C
X434	F	836	2	48.2	D	64.2	$8.47x10^3$	pgm^+, C
X421	F	568	2	45.4	D	67.4	$3.76x10^3$	pgm^+, C
X711	F	516	2	44.9	D	68.8	$4.37x10^4$	o, C
X770	F	322	2	43.0	D	66.0	$6.23x10^4$	pgm^+, C
X759	F	288	2	45.7	D	90.4	$2.14x10^7$	pgm^+
X511	F	233	2	49.5	D	65.5	$3.97x10^4$	pgm^+, C
X606	M	106	2	44.5	D	89.2	$2.54x10^4$	pgm^+

[a] Fever was defined as the first of three consecutive hourly measurements at least 1.5°C above their respective baseline averages at the same hour of the day. For Animal X515 some telemetry readings were not available. The time reported was the first time a three hour block was over the limit, but the middle hour measurement was missing

[b] C = contamination present; D = died; o = negative for pigmented *Y. pestis;* pgm^+ = positive for pigmented *Y. pestis*

[c] time to death was taken from telemetry data or clinical observation

[d] last bacteremia is from the last daily blood draw, not a terminal sample

Animals on this study were all bacteremic by the Day 2 blood draw, ranging from 33 to 657,000 CFU/mL (Table 6). A terminal sample was taken from all animals and was analyzed only by qualitative streaking on Congo red agar; nine of the terminal samples contained pigmented *Y. pestis* (all except X711). Terminal nasopharyngeal discharge and lung fluid were also analyzed by streaking on Congo red agar and all samples obtained were positive for *Y. pestis*. Contamination with unidentified bacteria was observed in 7 of the terminal blood samples, 3 of the nasopharyngeal washes, and one of the lung washes. The source and nature of the bacterial contaminant(s) were not identified in this study.

Fever was not prospectively defined for this first pneumonic plague study in this laboratory. Telemetry recordings indicated that all animals initiated a fever between 1.5 and 2.0 days, with a sustained body temperature of about 41°C around 2 days post-challenge. Heart rate increased around 2 days post-challenge, accompanied by slight increases in blood pressure and a marked increase in respiratory rate. All animals died, between 2.5 and 4.0 days post-challenge. Based

on the clinical symptomatology, the cause of death in all ten animals was concluded to be pneumonic plague.

A complete gross necropsy was performed on all animals and all findings were recorded. The most prominent pathologic findings are recorded in Table 7. The following tissues were collected at necropsy and fixed in 10% neutral buffered formalin: lungs, intrathoracic lymph nodes, and gross lesions. Collected tissues were examined histopathologically as needed to confirm the cause of death. There were no findings in brain following microscopic examination in any animals. Animal X106 was noted to have fibrin thrombi in renal glomerular capillaries, consistent with disseminated intravascular coagulopathy.

Table 7 617-G607610 Natural History: Summary of Prominent Gross and Microscopic Findings

Animal ID	Sex	Challenge Dose, LD_{50} equivalents	Gross Findings		Microscopic Findings					
			Lung, discoloration/nodule/ mass	Thoracic Cavity fluid, mL	Lung, inflammation	Lung, bacteria[b]	Bronchial Lymph Node, bacteria	Mediastinal Lymph Node, bacteria	Spleen, bacteria	Kidney, glomerulus, fibrin
X396	M	1150	NGO	15	++	++/+++	+++	++++	+++	NMO
X106	M	1094	++[a]	15	+++	++/++++	++++	++++	NMO	+
X515	F	1024	NGO	3	++	++/++++	+++	++	NMO	NMO
X434	F	836	NGO	20	++	++/+++	+++	++	+++	NMO
X421	F	568	NGO	7	++	++/++	++++	++	++++	NMO
X711	F	516	NGO	15	++	++/+++	++	++	+	NMO
X770	F	322	NGO	10	++	++/+++	++++	+++	++	NMO
X759	F	288	++	10	++++	+/++++	++	NMO	+	NMO
X511	F	233	NGO	15	++	+/++	+++	++	+++	NMO
X606	M	106	++++	NGO	++++	++/++++	++	++	++	NMO

[a] Severity: ++++ = marked; +++ = moderate; ++ = mild; + = minimal; NGO = no gross observation; NMO = no microscopic observation

[b] † observations are intracellular/extracellular bacteria.

The progression of untreated pneumonic plague in AGMs following aerosol exposure to *Y. pestis* was confirmed in the first, non-GLP study at BBRC. The challenge dose exceeded the target in all but one animal; however the clinical signs and pathology are the same as that reported in the other natural history studies, though the time course of disease is somewhat shorter. Animals presented with fever earlier than in other studies and the average time to death was somewhat shorter, Day 3 rather than Day 4. This study was repeated after additional work to refine the aerosol challenge conditions to achieve the target challenge dose.

1.4 Natural Course of Untreated Pneumonic Plague in African Green Monkeys (Study No. 875-G607610)

The objective of this study (875-G607610) was the assessment of pneumonic plague disease through clinical observations, blood analyses and telemetric monitoring of physiological parameters of AGMs infected with aerosolized *Y. pestis*. This study was intended to confirm the course of disease seen in previous studies with a target challenge dose of 100 LD_{50} equivalents, in preparation for antibiotic efficacy studies. Ten experimentally naïve, healthy, adult AGMs (5 male, 5 female) with target weights of 3.5 to 6.0 kg were placed on study. Prior to challenge, the animals had telemetry devices implanted, and baseline telemetry data were collected, with average readings obtained every 15 minutes for 13 days. Clinical observations were recorded twice daily. Clinical chemistry, hematology and coagulation indices were also assessed prior to challenge, on Day 0. A *Yersinia* antigen enzyme-linked immunosorbent assay (ELISA) was also performed to ensure that animals were naïve to *Yersinia*; no animals were excluded from study.

The challenge material, *Y. pestis* CO92, was prepared in the same manner as Study 617-G607610. Briefly, pigmented colonies from fresh Congo red agar plates were inoculated into heart infusion broth and grown to saturation at 26°C. Bacteria were washed and resuspended at the desired concentration and held on ice prior to aerosolization.

On the day of challenge, an aerosol pre-run was performed without an animal, and the resulting aerosol was analyzed by flow cytometry after staining with a fluorescent vital dye. AGMs were anesthetized and then exposed to the *Y. pestis* aerosol in a head-only chamber in a Class III biosafety cabinet, with a target dose of 100 LD_{50} equivalents. Minute volume was measured by whole-body plethysmography in real time during the challenge. Each animal's actual challenge dose was verified retrospectively by collecting the aerosol during the challenge in an all glass impinger and quantifying organisms by plating dilutions. All animal challenges were performed on a single day over a three hour period.

After challenge, clinical observations were recorded three times daily along with continuous telemetry monitoring. Blood was obtained daily for bacteremia, hematology, clinical chemistry and coagulation. Bacteremia was determined both quantitatively, by serial dilution and plating on tryptic soy agar, and qualitatively, by direct streaking on Congo red agar and *Yersinia* selective agar. Blood was also mixed with tryptic soy broth and incubated for streaking of enriched cultures on Congo red and *Yersinia* selective agar.

Actual challenge doses delivered in this study ranged from 24 to 88 LD_{50} equivalents with a mean of 48 ± 23 LD_{50} equivalents. These data are summarized in Table 8 along with fever, bacteremia and survival data. The individual animal spray factors, and therefore challenge doses, were much tighter on this study than Study 617-G607610. Based on clinical symptomatology, all ten animals were concluded to have succumbed to pneumonic plague. On Day 2, three animals were bacteremic by both quantitative and qualitative assessment, whereas an additional 4 animals were bacteremic by qualitative assessment only, two of which showed colonies on the quantitative plates but below the accepted counting range (25 to 300 colonies per plate). All animals were bacteremic by Day 3, by both qualitative and quantitative assays.

Fever, as defined by an increase of >1.5°C over baseline, was seen between 48 and 62 hours in all animals. All animals died naturally between Day 3 and Day 6 and underwent gross necropsy and histopathology of selected tissues.

Table 8 875-G607610 Natural History: Challenge Dose, Survival, Fever and Bacteremia Observations

Animal ID	Sex	Challenge Dose, LD_{50} equivalents	1st Bacteremia, day[a]	Time to Fever, hours[b]	Outcome[c]	Time to Death, hours	Terminal Bacteremia, CFU/mL
Y256	M	88	2	50	D	66.3	$1.03x10^9$
X753	F	76	3	61	D	102.6	$7.43x10^6$
Y213	F	76	3	58	D	77.6	$2.41x10^8$
X486	M	43	2†	59	D	87.5	$8.03x10^7$
X603	F	38	2†	52	D	88.2	$2.16x10^9$
W904	F	38	2~	55	D	112.3	$3.43x10^5$
X900	M	37	3	62	D	139.0	$8.63x10^6$
Y212	F	36	2~	56	D	74.0	$4.73x10^7$
X950	M	25	2	51	D	84.7	$1.16x10^9$
X840	M	24	2	48	D	100.4	$7.23x10^7$

[a] by both qualitative and quantitative methods, unless indicated otherwise, † positive by both methods but below 250 CFU/mL, ~ positive only by qualitative method
[b] Fever was defined as body temperature >1.5°C above baseline average
[c] D = died naturally

A complete gross necropsy was performed on all animals and all findings were recorded. The following tissues were collected at necropsy and fixed in 10% neutral buffered formalin: lungs and bronchi, bronchial and mediastinal lymph nodes and gross lesions. These tissues were evaluated microscopically. Selected gross and microscopic findings are summarized in Table 9. Prominent findings seen in 9 of 10 animals at gross necropsy were thoracic cavity fluid and observations such as foci, discoloration, nodules and/or masses in lungs. Microscopic findings included bacteria in all animals in lungs as well as tracheobronchial and mediastinal lymph nodes. Only one animal exhibited macroscopic findings in the brain, confirmed microscopically by the presence of bacteria.

Table 9 875-G607610 Natural History: Summary of Prominent Pathologic Findings

Animal ID	Sex[a]	Challenge Dose, LD_{50} equivalents	Gross Findings		Microscopic Findings			
			Thoracic Cavity fluid (mL)	Lung: focus, discoloration, nodule, mass[b]	Lung, bacteria	Bronchial Lymph node, bacteria	Mediastinal lymph node, bacteria	Brain, meninges, bacteria with fibrin exudation
Y256	M	88	10	Y	++[d]	+++	+	NE[c]
X753	F	76	30	Y	+++	+++	++	NE
Y213	F	76	40	N	+	++	+++	NE
X486	M	43	40	Y	++	+	+++	NE
X603	F	38	8	Y	++	+++	+	NE
W904	F	38	NGO[e]	Y	++++	++	++	NE
X900	M	37	10	Y	++++	++++	++	NE
Y212	F	36	30	Y	+	++	++	NE
X950	M	25	30	Y	++	+++	++	+/++
X840	M	24	25	Y	++++	++	+	NE

[a] F = female; M = male.
[b] Y = yes, N = no.
[c] NE, not examined.
[d] Severity: ++++ = marked; +++ = moderate; ++ = mild; + = minimal.
[e] NGO = no gross observation.

The progression of untreated pneumonic plague in AGMs following aerosol exposure was documented in this non-GLP study. Animals presented with fever and bacteremia in a time frame similar to other natural history studies conducted with this challenge dose. This target challenge dose results in a disease time course that could potentially be effectively treated with timely administration of effective antibiotics.

1.5 Summary of the African Green Monkey (AGM) Model of Pneumonic Plague

In summary, the series of studies described here are the first studies conducted to establish the non-human primate (AGM) animal model for the evaluation of antibiotic treatment of pneumonic plague disease. The objectives of the studies conducted in support of the animal model were successfully achieved and established the natural history of disease progression in the AGM.

2 Comparison of Human and Animal (African Green Monkey) Natural Courses of Pneumonic Plague

DMID/NIAID has studied the exposure of AGMs to *Y. pestis* in several nonclinical studies as described above. In order to support that the AGM is a well-characterized animal model for predicting response in human pneumonic plaque, a comparison of the characteristics of human disease using the literature and the data obtained in the nonclinical studies with regard to clinical signs and symptoms, pathophysiology, disease progression, radiology, and histopathology are presented in this section. A fair comparison of natural cases of pneumonic plague in humans to experimental infections of AGMs requires recognition of the limitations of comparisons and differences between these diseases. The human cases summarized are based on the diagnosis of pneumonic plague rather than route of exposure. While the route of exposure and timing can be surmised from some of the human case reports, it is not always known. For human cases of inhaled *Y. pestis*, the dose is unknown, while the dose in AGMs was measured. The inhaled dose (CFU) of *Y. pestis* varies from animal to animal based on respiratory minute volume; however, it is likely to be equal to or greater than the level of exposure in the human cases. The timing of signs and symptoms in human cases are sometimes described relative to the first sign or symptom and sometimes relative to the time of presumptive exposure; whereas, timing in the animal studies is always relative to exposure. Clinical symptomatology, such as headache, chills, and myalgia, are not obtainable in animal studies, and therefore, no comparison can be made. While descriptions of the course of human disease demonstrated variability in presentation or care-seeking behavior, the animal studies are conducted in controlled, laboratory settings which results in less apparent variability as presentation is not a variable.

In Wu Lien-Teh's 1926 treatise,[61] the time course of human disease was reported to be 2 to 9 days, with the majority of cases being 2 to 5 or 6 days. All other case studies presented here fit within the overall time frame of 2 to 9 days. This time course matches exactly that seen in the AGM studies summarized here and in the literature (i.e., 2 to 9 days)[15].

Fever is a clinical sign noted consistently in both humans and AGMs. Among the human cases reviewed in the literature, only a few descriptions made no mention of fever: Dr. Manser's nurse, and two of the three refugees whose descriptions only refer to suspicion of plague or the lack of plague-like symptoms. All other cases noted a fever. This is consistent with the AGM model, in which all animals present with a fever, typically at 72 hours post-exposure. The most compelling human case description that determined the interval between exposure and fever is the wildlife biologist exposed during necropsy of a mountain lion, where the time to fever was 3 days.[59] This coincides with the time to fever seen in the AGM studies.

Most human cases reviewed in the literature were confirmed as pneumonic plague based on the presence of *Y. pestis* bacilli found in sputum rather than blood. The AGM model correlated fever with the presence of bacteria in the blood; however, observations of in these studies of sputum or frothy discharge from nares, with or without blood, are consistent with the progression of cough in human disease. Both of the Battelle natural history studies cultured fluid from the lung and nasal discharge for the presence of *Y. pestis*. In all 20 animals, *Y. pestis* was found at death in both nasal discharge and lung fluids.

Heart rate and respiratory rate were noted in the clinical summaries to be elevated during the course of disease, particularly in the cases followed by Chun[11,12] and Wu Lien-The.[61] These observations were typically made daily, while in the AGM studies, they were monitored continuously via telemetry, except for respiratory rate in study F03-09G, which was measured visually, though frequently. The increased respiratory rate tends to be more dramatic in late disease in both human and AGM cases. Heart rate is also increased in both humans and AGMs.

In humans, changes in pulmonary function were mainly gathered through auscultation. Although auscultation was not performed in the AGM, the character of respiration was assessed during scheduled and frequent observations. Rales were observed in both humans and AGMs; 3 of 4 diseased animals in study F03-09G had rales just prior to euthanasia/death. Chest radiographs were performed in 2 AGM studies (F03-09G and FY06-126) and were summarized in NIAID's Independent Review of Radiology (see FDA briefing document). Pulmonary infiltrates in AGMs were mild to moderate on Day 3 and severe at the time of death. This is consistent with the clinical radiological findings reported by Alsofrom et al.,[1] where 8 of 9 cases were reported as bilateral pulmonary infiltrates, compared to approximately 65% in AGMs.

There are few published reports of human pathology,[18,58,59] and macroscopic and microscopic pathology findings are very similar in human and AGM cases of pneumonic plague. Pathology findings reported in humans were: lobar to sublobar pulmonary consolidation (3 of 3), inflammatory infiltrates (neutrophils with fibrin) (2 of 3), hemorrhagic and frothy fluid in both lungs (1 of 3), pulmonary exudates and effusions (1 of 3), bronchopneumonia (1 of 3), and the presence of bacilli (2 of 3). Note that these findings are taken directly from a small number of published reports and were not independently determined. The most prominent pulmonary findings in the independent review of 36 untreated AGMs were bacteria, edema, hemorrhage, inflammatory infiltrate (intra-alveolar neutrophils followed by macrophages), and pleural fibrin. These pathology findings are essentially indistinguishable.

Table 10 summarizes a comparison of the main features of pneumonic plague between humans and AGMs.

Table 10 Human and African Green Monkey Natural Courses of Pneumonic Plague

	Human[a]	African Green Monkey[b]
Time course of disease, days	2 to 9	2 to 9
Temperature	Elevated in ~100% of cases (at 3 days in 1 case)	Elevated in 100% of cases (typically 3 days post-exposure)
Yersinia pestis present	Positive in 100% of sputum	Positive in 100% of blood and/or lung/nasal fluids
Heart rate	Elevated	Elevated[c]
Respiration rate	Elevated late in disease	Elevated late in disease
Chest radiographs	Pulmonary infiltrates 90% bilateral	Pulmonary infiltrates Approximately 65% bilateral[c]
Pathology, lung	Consolidations, Inflammatory infiltrates, Hemorrhagic/frothy fluid, Exudates and effusions, Bronchopneumonia, Bacilli	Bacteria, Edema, Hemorrhage, Inflammatory infiltrates/bronchopneumonia, Pleural fibrin

[a] Data from 3 cases in 3 publications [18,58,59]

[b] Data from 34 untreated AGMs from 4 studies (F03-09G, FY06-126, 617-G607610, and 875-G607610) and Davis, 1996[15]

[c] Heart rate and radiograph data from F03-09G and FY06-126

Clinical signs/tests that could potentially serve as a trigger for treatment were bacteremia, body temperature, heart rate, and respiratory rate; chest radiographs were also considered though are not possible at all study sites. Body temperature, heart rate, respiratory rate and chest radiographs can be real-time triggers, but bacteremia requires at least 18-24 hours of culture. It is also worth noting that bacteremia and chest radiographs are limited in frequency due to animal welfare concerns about blood volume and anesthesia, while body temperature, heart rate and respiratory rate, were monitored continuously by telemetry. In practice, chest radiographs were obtained upon the appearance of other signs such as increased respirations or body temperature. Body temperature, heart rate, respiratory rate and chest radiographs are all general signs and only bacteremia is specific to *Yersinia pestis* infection. Therefore, it was important to determine the correlation of bacteremia with other clinical signs. Comparing body temperature, heart rate and respiratory rate as possible treatment triggers, body temperature increased significantly and maximally early, while increases in heart and respiratory rates began at the same time and continued to increase as disease severity progressed, with maximal levels appearing late in disease. Two challenged survivors never exhibited increased body temperature, heart or respiratory rates and were also never bacteremic. Initial chest radiographs, at the time of first clinical signs (fever) were abnormal (predominately mild) and increased in severity until death (moderate to marked/severe). Therefore, fever was selected as the treatment trigger for subsequent studies of antibiotic efficacy.

3. Summary

In summary, based on the clinical case descriptions reported in the literature and the data obtained from four studies conducted in the AGM, the clinical presentations in untreated human cases and in the AGM are strikingly similar. In the context of the Animal Rule, there is a

reasonably well understood pathophysiological mechanism for the toxicity of *Yersinia pestis*, which is similar between humans and AGMs with death attributable to bronchopneumonia. Given the four natural history studies conducted in AGMs, this model is sufficiently well characterized and has been adequately evaluated for its response to *Yersinia pestis*. A comparison reveals no differences that would suggest that the AGM model is a less-than-satisfactory model of human pneumonic plague. The primary endpoint in the studies conducted in the AGM is clearly related to the desired benefit in humans, that is survival. Therefore, the AGM model is considered to be a well-characterized model for the testing of antibiotics that may have utility as treatment options in humans following known or suspected exposure to *Y. pestis*; this satisfies the requirements under the Code of Federal Regulations (CFR), Animal Rule (21 CFR 314.610).

Attachment 2

Attachment 2

Current LEVAQUIN USPI (dated Oct 2011)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEVAQUIN® safely and effectively. See full prescribing information for LEVAQUIN.

LEVAQUIN® (levofloxacin) Tablet, Film Coated for Oral use
LEVAQUIN® (levofloxacin) Solution for Oral use
LEVAQUIN® (levofloxacin) Injection, Solution, Concentrate for Intravenous use
LEVAQUIN® (levofloxacin) Injection, Solution for Intravenous use
Initial U.S. Approval: 1996

WARNING:
Fluoroquinolones, including LEVAQUIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants *[See Warnings and Precautions (5.1)]*.
Fluoroquinolones, including LEVAQUIN®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis *[See Warnings and Precautions (5.2)]*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of LEVAQUIN® and other antibacterial drugs, LEVAQUIN® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

——————RECENT MAJOR CHANGES——————

Warnings and Precautions
- Exacerbation of myasthenia gravis (5.2) 01/2011
- Increased intracranial pressure (pseudotumor cerebri) (5.6) 10/2011

——————INDICATIONS AND USAGE——————

LEVAQUIN® is a fluoroquinolone antibacterial indicated in adults (≥18 years of age) with infections caused by designated, susceptible bacteria (1, 12.4).
- Pneumonia: nosocomial (1.1) and community acquired (1.2, 1.3)
- Acute bacterial sinusitis (1.4)
- Acute bacterial exacerbation of chronic bronchitis (1.5)
- Skin and skin structure infections: complicated (1.6) and uncomplicated (1.7)
- Chronic bacterial prostatitis (1.8)
- Urinary tract infections: complicated (1.9, 1.10) and uncomplicated (1.12)
- Acute pyelonephritis (1.11)
- Inhalational anthrax, post-exposure (1.13). Not tested in humans for post-exposure prevention of inhalational anthrax; plasma concentrations are likely to predict efficacy (14.9)

——————DOSAGE AND ADMINISTRATION——————

- Dosage in patients with normal renal function (2.1)

Type of Infection	Dose Every 24 hours	Duration (days)
Nosocomial Pneumonia (1.1)	750 mg	7–14
Community Acquired Pneumonia (1.2)	500 mg	7–14
Community Acquired Pneumonia (1.3)	750 mg	5
Acute Bacterial Sinusitis (1.4)	750 mg	5
	500 mg	10–14
Acute Bacterial Exacerbation of Chronic Bronchitis (1.5)	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI) (1.6)	750 mg	7–14
Uncomplicated SSSI (1.7)	500 mg	7–10
Chronic Bacterial Prostatitis (1.8)	500 mg	28
Complicated Urinary Tract Infection (1.9) or Acute Pyelonephritis (1.11)	750 mg	5
Complicated Urinary Tract Infection (1.10) or Acute Pyelonephritis (1.11)	250 mg	10
Uncomplicated Urinary Tract Infection (1.12)	250 mg	3
Inhalational Anthrax (Post-Exposure) (1.13)		
Adults and Pediatric Patients > 50 kg and ≥ 6 months of age	500 mg	60
Pediatric Patients < 50 kg and ≥ 6 months of age	8 mg/kg BID (not to exceed 250 mg/dose)	60

- Adjust dose for creatinine clearance < 50 mL/min (2.3, 8.6, 12.3)
- IV Injection, Single-Use or Premix: Slow IV infusion only, over 60 or 90 minutes depending on dose. Avoid rapid or bolus IV (2.5)
- Dilute single-use vials to 5 mg/mL prior to IV infusion (2.6)
- Do not mix with other medications in vial or IV line (2.6)

——————DOSAGE FORMS AND STRENGTHS——————

Formulation (3)	Strength
Tablets	250 mg, 500 mg, and 750 mg
Oral Solution	25 mg/mL
Injection: single-use vials for dilution	500 mg in 20 mL 750 mg in 30 mL
Injection: premix single-use flexible containers	250 mg in 50 mL 500 mg in 100 mL 750 mg in 150 mL

——————CONTRAINDICATIONS——————

Known hypersensitivity to LEVAQUIN® or other quinolones (4, 5.3)

——————WARNINGS AND PRECAUTIONS——————

- Risk of tendinitis and tendon rupture is increased. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroids, and in patients with kidney, heart or lung transplants. Discontinue if pain or inflammation in a tendon occurs (5.1, 8.5)
- May exacerbate muscle weakness in persons with myasthenia gravis. Avoid use in patients with a known history of myasthenia gravis (5.2).
- Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose (4,5.3)
- Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses (5.4)
- Hepatotoxicity: Severe, and sometimes fatal, hepatoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur (5.5)
- Central nervous system effects, including convulsions, anxiety, confusion, depression, and insomnia may occur after the first dose. Use with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold. . Increased intracranial pressure (pseudotumor cerebri) has been reported (5.6)
- *Clostridium difficile*-associated colitis: evaluate if diarrhea occurs (5.7)
- Peripheral neuropathy: discontinue if symptoms occur in order to prevent irreversibility (5.8)
- Prolongation of the QT interval and isolated cases of torsade de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval (5.9, 8.5)

——————ADVERSE REACTIONS——————

The most common reactions (≥3%) were nausea, headache, diarrhea, insomnia, constipation and dizziness (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

——————DRUG INTERACTIONS——————

Interacting Drug	Interaction
Multivalent cation-containing products including antacids, metal cations or didanosine	Absorption of levofloxacin is decreased when the tablet or oral solution formulation is taken within 2 hours of these products. Do not co-administer the intravenous formulation in the same IV line with a multivalent cation, e.g., magnesium (2.4, 7.1)

1

Interacting Drug	Interaction
Warfarin	Effect may be enhanced. Monitor prothrombin time, INR, watch for bleeding (7.2)
Antidiabetic agents	Carefully monitor blood glucose (5.11, 7.3)

——————USE IN SPECIFIC POPULATIONS——————

- **Geriatrics:** Severe hepatotoxicity has been reported. The majority of reports describe patients 65 years of age or older (5.5, 8.5, 17). May have increased risk of tendinopathy (including rupture), especially with concomitant corticosteroid use (5.1, 8.5, 17). May be more susceptible to prolongation of the QT interval. (5.9, 8.5, 17).
- **Pediatrics:** Musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) seen in more LEVAQUIN®-treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals (5.10, 8.4, 13.2). Safety in pediatric patients treated for more than 14 days has not been studied. Risk-benefit appropriate only for the treatment of inhalational anthrax (post-exposure) (1.13, 2.2, 8.4, 14.9)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING:

Fluoroquinolones, including LEVAQUIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants *[See Warnings and Precautions (5.1)]*.

Fluoroquinolones, including LEVAQUIN®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of LEVAQUIN® and other antibacterial drugs, LEVAQUIN® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

LEVAQUIN® Tablets/Injection and Oral Solution are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed in this section. LEVAQUIN® Injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form).

Culture and susceptibility testing

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin *[see Clinical Pharmacology (12.4)]*. Therapy with LEVAQUIN® may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with LEVAQUIN®. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

1.1 Nosocomial Pneumonia

LEVAQUIN® is indicated for the treatment of nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended *[see Clinical Studies (14.1)]*.

1.2 Community-Acquired Pneumonia: 7–14 day Treatment Regimen

LEVAQUIN® is indicated for the treatment of community-acquired pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae* (including multi-drug-resistant *Streptococcus pneumoniae* [MDRSP]), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae [see Dosage and Administration (2.1) and Clinical Studies (14.2)]*.

MDRSP isolates are strains resistant to two or more of the following antibacterials: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

1.3 Community-Acquired Pneumonia: 5-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae* (excluding multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae [see Dosage and Administration (2.1)* and *Clinical Studies (14.3)]*.

1.4 Acute Bacterial Sinusitis: 5-day and 10–14 day Treatment Regimens

LEVAQUIN® is indicated for the treatment of acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis [see Clinical Studies (14.4)]*.

1.5 Acute Bacterial Exacerbation of Chronic Bronchitis

LEVAQUIN® is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis*.

1.6 Complicated Skin and Skin Structure Infections

LEVAQUIN® is indicated for the treatment of complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, or *Proteus mirabilis [see Clinical Studies (14.5)]*.

1.7 Uncomplicated Skin and Skin Structure Infections

LEVAQUIN® is indicated for the treatment of uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible *Staphylococcus aureus*, or *Streptococcus pyogenes*.

1.8 Chronic Bacterial Prostatitis

LEVAQUIN® is indicated for the treatment of chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, or methicillin-susceptible *Staphylococcus epidermidis [see Clinical Studies (14.6)]*.

1.9 Complicated Urinary Tract Infections: 5-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis [see Clinical Studies (14.7)]*.

1.10 Complicated Urinary Tract Infections: 10-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa [see Clinical Studies (14.8)]*.

1.11 Acute Pyelonephritis: 5 or 10-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of acute pyelonephritis caused by *Escherichia coli*, including cases with concurrent bacteremia *[see Clinical Studies (14.7*, *14.8)]*.

1.12 Uncomplicated Urinary Tract Infections

LEVAQUIN® is indicated for the treatment of uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Staphylococcus saprophyticus*.

1.13 Inhalational Anthrax (Post-Exposure)

LEVAQUIN® is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. The effectiveness of LEVAQUIN® is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. LEVAQUIN® has not been tested in humans for the post-exposure prevention of inhalation anthrax. The safety of LEVAQUIN® in adults for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged LEVAQUIN® therapy should only be used when the benefit outweighs the risk *[see Dosage and Administration (2.1*, *2.2) and Clinical Studies (14.9)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Patients with Normal Renal Function

The usual dose of LEVAQUIN® Tablets or Oral Solution is 250 mg, 500 mg, or 750 mg administered orally every 24 hours, as indicated by infection and described in Table 1. The usual dose of LEVAQUIN® Injection is 250 mg or 500 mg administered by slow infusion over 60 minutes every 24 hours or 750 mg administered by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in Table 1.

These recommendations apply to patients with creatinine clearance ≥ 50 mL/min. For patients with creatinine clearance <50 mL/min, adjustments to the dosing regimen are required *[see Dosage and Administration (2.3)]*.

Table 1: Dosage in Adult Patients with Normal Renal Function (creatinine clearance ≥ 50 mL/min)

Type of Infection[*]	Dosed Every 24 hours	Duration (days)[†]
Nosocomial Pneumonia	750 mg	7–14
Community Acquired Pneumonia[‡]	500 mg	7–14
Community Acquired Pneumonia[§]	750 mg	5
Acute Bacterial Sinusitis	750 mg	5
	500 mg	10–14
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7–14
Uncomplicated SSSI	500 mg	7–10
Chronic Bacterial Prostatitis	500 mg	28
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[¶]	750 mg	5
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[#]	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Inhalational Anthrax (Post-Exposure), adult and pediatric patients > 50 kg and ≥ 6 months of age[Þ,ß]	500 mg	60[ß]
Pediatric patients < 50 kg and ≥ 6 months of age[Þ,ß]	see Table 2 below (2.2)	60[ß]

[*] Due to the designated pathogens *[see Indications and Usage (1)]*.

[†] Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.

[‡] Due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila*, or *Mycoplasma pneumoniae [see Indications and Usage (1.2)]*.

[§] Due to *Streptococcus pneumoniae* (excluding multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae*, *or Chlamydophila pneumoniae [see Indications and Usage (1.3)]*.

[¶] This regimen is indicated for cUTI due to *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and AP due to *E. coli*, including cases with concurrent bacteremia.

[#] This regimen is indicated for cUTI due to *Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa*; and for AP due to *E. coli*.

[Þ] Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit *[see Clinical Studies (14.9)]*.

[ß] The safety of LEVAQUIN® in adults for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients *[see Warnings and Precautions (5.10)*, *Use in Specific Populations (8.4)*, *and Clinical Studies (14.9)]*. Prolonged LEVAQUIN® therapy should only be used when the benefit outweighs the risk.

2.2 Dosage in Pediatric Patients

The dosage in pediatric patients ≥ 6 months of age is described below in Table 2.

Table 2: Dosage in Pediatric Patients ≥ 6 months of age

Type of Infection*	Dose	Freq. Once every	Duration†
Inhalational Anthrax (post-exposure)‡,§			
Pediatric patients > 50 kg and ≥ 6 months of age	500 mg	24 hr	60 days§
Pediatric patients < 50 kg and ≥ 6 months of age	8 mg/kg (not to exceed 250 mg per dose)	12 hr	60 days§

* Due to *Bacillus anthracis [see Indications and Usage (1.13)]*
† Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.
‡ Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit *[see Clinical Studies (14.9)]*
§ The safety of LEVAQUIN® in pediatric patients for durations of therapy beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients *[see Warnings and Precautions (5.10), Use in Specific Populations (8.4), and Clinical Studies (14.9)]*. Prolonged LEVAQUIN® therapy should only be used when the benefit outweighs the risk.

2.3 Dosage Adjustment in Adults with Renal Impairment

Administer LEVAQUIN® with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced.

No adjustment is necessary for patients with a creatinine clearance ≥ 50 mL/min.

In patients with impaired renal function (creatinine clearance <50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance *[see Use in Specific Populations (8.6)]*.

Table 3 shows how to adjust dose based on creatinine clearance.

Table 3: Dosage Adjustment in Adult Patients with Renal Impairment (creatinine clearance <50 mL/min)

Dosage in Normal Renal Function Every 24 hours	Creatinine Clearance 20 to 49 mL/min	Creatinine Clearance 10 to 19 mL/min	Hemodialysis or Chronic Ambulatory Peritoneal Dialysis (CAPD)
750 mg	750 mg every 48 hours	750 mg initial dose, then 500 mg every 48 hours	750 mg initial dose, then 500 mg every 48 hours
500 mg	500 mg initial dose, then 250 mg every 24 hours	500 mg initial dose, then 250 mg every 48 hours	500 mg initial dose, then 250 mg every 48 hours
250 mg	No dosage adjustment required	250 mg every 48 hours. If treating uncomplicated UTI, then no dosage adjustment is required	No information on dosing adjustment is available

2.4 Drug Interaction With Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN® Tablets and Oral Solution

LEVAQUIN® Tablets and Oral Solution should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine chewable/buffered tablets or the pediatric powder for oral solution *[see Drug Interactions (7.1) and Patient Counseling Information (17.2)]*.

LEVAQUIN® Injection

LEVAQUIN® Injection should not be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line *[see Dosage and Administration (2.6)]*.

2.5 Administration Instructions

Food and LEVAQUIN® Tablets and Oral Solution

LEVAQUIN® Tablets can be administered without regard to food. It is recommended that LEVAQUIN® Oral Solution be taken 1 hour before or 2 hours after eating.

LEVAQUIN® Injection

Caution: Rapid or bolus intravenous infusion of LEVAQUIN® has been associated with hypotension and must be avoided. LEVAQUIN® Injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage. LEVAQUIN® Injection should be administered only by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Hydration for Patients Receiving LEVAQUIN® Tablets, Oral Solution, and Injection

Adequate hydration of patients receiving oral or intravenous LEVAQUIN® should be maintained to prevent the formation of highly concentrated urine. Crystalluria and cylindruria have been reported with quinolones *[see Adverse Reactions (6.1) and Patient Counseling Information (17.2)]*.

2.6 Preparation of Intravenous Product

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Because only limited data are available on the compatibility of LEVAQUIN® Injection with other intravenous substances, additives or other medications should not be added to LEVAQUIN® Injection Premix in Single-Use Flexible Containers and LEVAQUIN® Injection in Single-Use Vials, or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN® Injection with an infusion solution compatible with LEVAQUIN® Injection and with any other drug(s) administered via this common line.

LEVAQUIN® Injection in Single-Use Vials

Single-use vials require dilution prior to administration.

LEVAQUIN® Injection is supplied in single-use vials containing a concentrated levofloxacin solution with the equivalent of 500 mg (20 mL vial) and 750 mg (30 mL vial) of levofloxacin in Water for Injection, USP. The 20 mL and 30 mL vials each contain 25 mg of levofloxacin/mL. These LEVAQUIN® Injection single-use vials must be further diluted with an appropriate solution prior to intravenous administration *[see Table 4]*. The concentration of the resulting diluted solution should be 5 mg/mL prior to administration.

Compatible Intravenous Solutions: Any of the following intravenous solutions may be used to prepare a 5 mg/mL levofloxacin solution with the approximate pH values:

Table 4: Compatible Intravenous Solutions

Intravenous Fluids	Final pH of LEVAQUIN® Solution
0.9% Sodium Chloride Injection, USP	4.71
5% Dextrose Injection, USP	4.58
5% Dextrose/0.9% NaCl Injection	4.62
5% Dextrose in Lactated Ringers	4.92
Plasma-Lyte® 56/5% Dextrose Injection	5.03
5% Dextrose, 0.45% Sodium Chloride, and 0.15% Potassium Chloride Injection	4.61
Sodium Lactate Injection (M/6)	5.54

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final intravenous solution. Since the vials are for single-use only, any unused portion remaining in the vial should be discarded. When used to prepare two 250 mg doses from the 20 mL vial containing 500 mg of levofloxacin, the full content of the vial should be withdrawn at once using a single-entry procedure, and a second dose should be

prepared and stored for subsequent use *[see Stability of LEVAQUIN® Injection Following Dilution]*.

Prepare the desired dosage of levofloxacin according to Table 5:

Table 5: Preparation of LEVAQUIN® Intravenous Solution

Desired Dosage Strength	From Appropriate Vial, Withdraw Volume	Volume of Diluent	Infusion Time
250 mg	10 mL (20 mL Vial)	40 mL	60 min
500 mg	20 mL (20 mL Vial)	80 mL	60 min
750 mg	30 mL (30 mL Vial)	120 mL	90 min

For example, to prepare a 500 mg dose using the 20 mL vial (25 mg/mL), withdraw 20 mL and dilute with a compatible intravenous solution to a total volume of 100 mL.

This intravenous drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Stability of LEVAQUIN® Injection Following Dilution: LEVAQUIN® Injection, when diluted in a compatible intravenous fluid to a concentration of 5 mg/mL, is stable for 72 hours when stored at or below 25°C (77°F) and for 14 days when stored under refrigeration at 5°C (41°F) in plastic intravenous containers. Solutions that are diluted in a compatible intravenous solution and frozen in glass bottles or plastic intravenous containers are stable for 6 months when stored at - 20°C (- 4°F). Thaw frozen solutions at room temperature 25°C (77°F) or in a refrigerator 8°C (46°F). Do not force thaw by microwave irradiation or water bath immersion. Do not refreeze after initial thawing.

LEVAQUIN® Injection Premix in Single-Use Flexible Containers (5 mg/mL)

LEVAQUIN® Injection is also supplied in flexible containers within a foil overwrap. These contain a premixed, ready to use levofloxacin solution in 5% dextrose (D5W) for single-use. The 100 mL premixed flexible containers contain either 250 mg/50 mL or 500 mg/100 mL of levofloxacin solution. The 150 mL flexible container contains 750 mg/150 mL of levofloxacin solution. The concentration of each container is 5 mg/mL. No further dilution of these preparations is necessary. Because the premix flexible containers are for single-use only, any unused portion should be discarded.

Instructions for the Use of LEVAQUIN® Injection Premix in Flexible Containers:

1. Tear outer wrap at the notch and remove solution container.
2. Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.

3. Do not use if the solution is cloudy or a precipitate is present.
4. Use sterile equipment.
5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Administration:

1. Close flow control clamp of administration set.
2. Remove cover from port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. **NOTE: See full directions on administration set carton.**
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of LEVAQUIN® Injection Premix in Flexible Containers.
6. Open flow control clamp to expel air from set. Close clamp.
7. Regulate rate of administration with flow control clamp.

3 DOSAGE FORMS AND STRENGTHS

TABLETS, Film-coated, capsule-shaped

- 250 mg terra cotta pink tablets, imprinted with "250" on one side and "LEVAQUIN" on the other
- 500 mg peach tablets, imprinted with "500" on one side and "LEVAQUIN" on the other
- 750 mg white tablets, imprinted with "750" on one side and "LEVAQUIN" on the other

ORAL SOLUTION, 25mg/mL, clear yellow to clear greenish-yellow color

INJECTION, Single-Use Vials of concentrated solution for dilution for intravenous infusion, clear yellow to clear greenish-yellow in appearance

- 20 mL vial of 25 mg/mL levofloxacin solution, equivalent to 500 mg of levofloxacin
- 30 mL vial of 25 mg/mL levofloxacin solution, equivalent to 750 mg of levofloxacin

INJECTION (5 mg/mL in 5% Dextrose) Premix in Single-Use Flexible Containers, for intravenous infusion

- 100 mL container, fill volume 50 mL (equivalent to 250 mg levofloxacin)
- 100 mL container, fill volume 100 mL (equivalent to 500 mg levofloxacin)
- 150 mL container, fill volume 150 mL (equivalent to 750 mg levofloxacin)

4 CONTRAINDICATIONS

LEVAQUIN® is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibacterials *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Tendinopathy and Tendon Rupture

Fluoroquinolones, including LEVAQUIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have been reported in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. LEVAQUIN® should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug. *[see Adverse Reactions (6.3)*; *Patient Counseling Information (17.3)]*.

5.2 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including LEVAQUIN®, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis *[see Adverse Reactions (6.3); Patient Counseling Information (17.3)]*.

5.3 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroquinolones, including LEVAQUIN®. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction

(including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. LEVAQUIN® should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated *[see Adverse Reactions (6)*; *Patient Counseling Information (17.3)]*.

5.4 Other Serious and Sometimes Fatal Reactions

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with fluoroquinolones, including LEVAQUIN®. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted *[see Adverse Reactions (6)*; *Patient Counseling Information (17.3)]*.

5.5 Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with LEVAQUIN®. No evidence of serious drug-associated hepatotoxicity was detected in clinical trials of over 7,000 patients. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. Most cases of severe hepatotoxicity were not associated with hypersensitivity *[see Warnings and Precautions (5.4)]*. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. LEVAQUIN® should be discontinued immediately if the patient develops signs and symptoms of hepatitis *[see Adverse Reactions (6)*; *Patient Counseling Information (17.3)]*.

5.6 Central Nervous System Effects

Convulsions, toxic psychoses, increased intracranial pressure (including pseudotumor cerebri) have been reported in patients receiving fluoroquinolones, including LEVAQUIN®. Fluoroquinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving LEVAQUIN®, the drug should be discontinued and appropriate measures instituted. As with other fluoroquinolones, LEVAQUIN® should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) *[see Adverse Reactions (6)*; *Drug Interactions (7.4*, *7.5)*; *Patient Counseling Information (17.3)]*.

5.7 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including LEVAQUIN®, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated *[see Adverse Reactions (6.2)*, *Patient Counseling Information (17.3)]*.

5.8 Peripheral Neuropathy

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including LEVAQUIN®. LEVAQUIN® should be discontinued if the patient experiences symptoms of neuropathy including pain, burning,

tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition *[see Adverse Reactions (6)*, *Patient Counseling Information (17.3)]*.

5.9 Prolongation of the QT Interval

Some fluoroquinolones, including LEVAQUIN®, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes have been spontaneously reported during postmarketing surveillance in patients receiving fluoroquinolones, including LEVAQUIN®. LEVAQUIN® should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval *[see Adverse Reactions (6.3)*, *Use in Specific Populations (8.5), and Patient Counseling Information (17.3)]*.

5.10 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

LEVAQUIN® is indicated in pediatric patients (≥6 months of age) only for the prevention of inhalational anthrax (post-exposure) *[see Indications and Usage (1.13)]*. An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving LEVAQUIN® *[see Use in Specific Populations (8.4)]*.

In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluoroquinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species *[see Animal Toxicology and/or Pharmacology (13.2)]*.

5.11 Blood Glucose Disturbances

As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with LEVAQUIN®, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with LEVAQUIN®, LEVAQUIN®

should be discontinued and appropriate therapy should be initiated immediately *[see Adverse Reactions (6.2)*; *Drug Interactions (7.3)*; *Patient Counseling Information (17.4)]*.

5.12 Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of fluoroquinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs *[see Adverse Reactions (6.3)*; *Patient Counseling Information (17.3)]*.

5.13 Development of Drug Resistant Bacteria

Prescribing LEVAQUIN® in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria *[see Patient Counseling Information (17.1)]*.

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Tendon Effects *[see Warnings and Precautions (5.1)]*
- Exacerbation of Myasthenia Gravis *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Other Serious and Sometimes Fatal Reactions *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Central Nervous System Effects *[see Warnings and Precautions (5.6)]*
- *Clostridium difficile*-Associated Diarrhea *[see Warnings and Precautions (5.7)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.8)]*
- Prolongation of the QT Interval *[see Warnings and Precautions (5.9)]*
- Musculoskeletal Disorders in Pediatric Patients *[see Warnings and Precautions (5.10)]*
- Blood Glucose Disturbances *[see Warnings and Precautions (5.11)]*
- Photosensitivity/Phototoxicity *[see Warnings and Precautions (5.12)]*
- Development of Drug Resistant Bacteria *[see Warnings and Precautions (5.13)]*

Hypotension has been associated with rapid or bolus intravenous infusion of LEVAQUIN®. LEVAQUIN® should be infused slowly over 60 to 90 minutes, depending on dosage *[see Dosage and Administration (2.5)]*.

Crystalluria and cylindruria have been reported with quinolones, including LEVAQUIN®. Therefore, adequate hydration of patients receiving LEVAQUIN® should be maintained to prevent the formation of a highly concentrated urine *[see Dosage and Administration (2.5)]*.

6.2 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to LEVAQUIN® in 7537 patients in 29 pooled Phase 3 clinical trials. The population studied had a mean age of 50 years (approximately 74% of the population was < 65 years of age), 50% were male, 71% were Caucasian, 19% were Black. Patients were treated with LEVAQUIN® for a wide variety of infectious diseases *[see Indications and Usage (1)]*. Patients received LEVAQUIN® doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily. Treatment duration was usually 3–14 days, and the mean number of days on therapy was 10 days.

The overall incidence, type and distribution of adverse reactions was similar in patients receiving LEVAQUIN® doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily. Discontinuation of LEVAQUIN® due to adverse drug reactions occurred in 4.3% of patients overall, 3.8% of patients treated with the 250 mg and 500 mg doses and 5.4% of patients treated with the 750 mg dose. The most common adverse drug reactions leading to discontinuation with the 250 and 500 mg doses were gastrointestinal (1.4%), primarily nausea (0.6%); vomiting (0.4%); dizziness (0.3%); and headache (0.2%). The most common adverse drug reactions leading to discontinuation with the 750 mg dose were gastrointestinal (1.2%), primarily nausea (0.6%), vomiting (0.5%); dizziness (0.3%); and headache (0.3%).

Adverse reactions occurring in ≥1% of LEVAQUIN®-treated patients and less common adverse reactions, occurring in 0.1 to <1% of LEVAQUIN®-treated patients, are shown in Table 6 and Table 7, respectively. The most common adverse drug reactions (≥3%) are nausea, headache, diarrhea, insomnia, constipation, and dizziness.

Table 6: Common (≥1%) Adverse Reactions Reported in Clinical Trials with LEVAQUIN®

System/Organ Class	Adverse Reaction	% (N=7537)
Infections and Infestations	moniliasis	1
Psychiatric Disorders	insomnia* *[see Warnings and Precautions (5.6)]*	4
Nervous System Disorders	headache dizziness *[see Warnings and Precautions (5.6)]*	6 3
Respiratory, Thoracic and Mediastinal Disorders	dyspnea *[see Warnings and Precautions (5.3)]*	1
Gastrointestinal Disorders	nausea diarrhea constipation abdominal pain vomiting dyspepsia	7 5 3 2 2 2
Skin and Subcutaneous Tissue Disorders	rash *[see Warnings and Precautions (5.3)]* pruritus	2 1
Reproductive System and Breast Disorders	vaginitis	1†
General Disorders and Administration Site Conditions	edema injection site reaction chest pain	1 1 1

* N=7274
† N=3758 (women)

Table 7: Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with LEVAQUIN® (N=7537)

System/Organ Class	Adverse Reaction
Infections and Infestations	genital moniliasis
Blood and Lymphatic System Disorders	anemia thrombocytopenia granulocytopenia *[see Warnings and Precautions (5.4)]*
Immune System Disorders	allergic reaction *[see Warnings and Precautions (5.3,5.4)]*
Metabolism and Nutrition Disorders	hyperglycemia hypoglycemia *[see Warnings and Precautions (5.11)]* hyperkalemia
Psychiatric Disorders	anxiety agitation confusion depression hallucination nightmare* *[see Warnings and Precautions (5.6)]* sleep disorder* anorexia abnormal dreaming*
Nervous System Disorders	tremor convulsions *[see Warnings and Precautions (5.6)]* paresthesia *[see Warnings and Precautions (5.8)]* vertigo hypertonia hyperkinesias abnormal gait somnolence* syncope
Respiratory, Thoracic and Mediastinal Disorders	epistaxis
Cardiac Disorders	cardiac arrest palpitation ventricular tachycardia ventricular arrhythmia
Vascular Disorders	phlebitis
Gastrointestinal Disorders	gastritis stomatitis pancreatitis esophagitis gastroenteritis glossitis pseudomembranous/ *C. difficile* colitis *[see Warnings and Precautions (5.7)]*
Hepatobiliary Disorders	abnormal hepatic function increased hepatic enzymes increased alkaline phosphatase

Table 7: Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with LEVAQUIN® (N=7537)

System/Organ Class	Adverse Reaction
Skin and Subcutaneous Tissue Disorders	urticaria *[see Warnings and Precautions (5.3)]*
Musculoskeletal and Connective Tissue Disorders	arthralgia tendinitis *[see Warnings and Precautions (5.1)]* myalgia skeletal pain
Renal and Urinary Disorders	 abnormal renal function acute renal failure *[see Warnings and Precautions (5.4)]*

* N = 7274

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with quinolones, including LEVAQUIN®. The relationship of the drugs to these events is not presently established.

6.3 Postmarketing Experience

Table 8 lists adverse reactions that have been identified during post-approval use of LEVAQUIN®. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Table 8: Postmarketing Reports Of Adverse Drug Reactions

System/Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	pancytopenia aplastic anemia leukopenia hemolytic anemia *[see Warnings and Precautions (5.4)]* eosinophilia
Immune System Disorders	hypersensitivity reactions, sometimes fatal including: anaphylactic/anaphylactoid reactions anaphylactic shock angioneurotic edema serum sickness *[see Warnings and Precautions (5.3,5.4)]*
Psychiatric Disorders	psychosis paranoia isolated reports of suicide attempt and suicidal ideation *[see Warnings and Precautions (5.6)]*

Table 8: Postmarketing Reports Of Adverse Drug Reactions

System/Organ Class	Adverse Reaction
Nervous System Disorders	exacerbation of myasthenia gravis *[see Warnings and Precautions (5.2)]* anosmia ageusia parosmia dysgeusia peripheral neuropathy *[see Warnings and Precautions (5.8)]* isolated reports of encephalopathy abnormal electroencephalogram (EEG) dysphonia pseudotumor cerebri *[see Warnings and Precautions (5.6)]*
Eye Disorders	vision disturbance, including diplopia visual acuity reduced vision blurred scotoma
Ear and Labyrinth Disorders	hypoacusis tinnitus
Cardiac Disorders	isolated reports of torsade de pointes electrocardiogram QT prolonged *[see Warnings and Precautions (5.9)]* tachycardia
Vascular Disorders	vasodilatation
Respiratory, Thoracic and Mediastinal Disorders	isolated reports of allergic pneumonitis *[see Warnings and Precautions (5.4)]*
Hepatobiliary Disorders	hepatic failure (including fatal cases) hepatitis jaundice *[see Warnings and Precautions (5.4),(5.5)]*
Skin and Subcutaneous Tissue Disorders	bullous eruptions to include: Stevens-Johnson Syndrome toxic epidermal necrolysis erythema multiforme *[see Warnings and Precautions (5.4)]* photosensitivity/phototoxicity reaction *[see Warnings and Precautions (5.12)]* leukocytoclastic vasculitis
Musculoskeletal and Connective Tissue Disorders	tendon rupture *[see Warnings and Precautions (5.1)]* muscle injury, including rupture rhabdomyolysis
Renal and Urinary Disorders	interstitial nephritis *[see Warnings and Precautions (5.4)]*
General Disorders and Administration Site Conditions	multi-organ failure pyrexia
Investigations	prothrombin time prolonged international normalized ratio prolonged muscle enzymes increased

7 DRUG INTERACTIONS

7.1 Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN® Tablets and Oral Solution

While the chelation by divalent cations is less marked than with other fluoroquinolones, concurrent administration of LEVAQUIN® Tablets and Oral Solution with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after oral LEVAQUIN® administration.

LEVAQUIN® Injection

There are no data concerning an interaction of intravenous fluoroquinolones with oral antacids, sucralfate, multivitamins, didanosine, or metal cations. However, no fluoroquinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line *[see Dosage and Administration (2.5)]*.

7.2 Warfarin

No significant effect of LEVAQUIN® on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. However, there have been reports during the postmarketing experience in patients that LEVAQUIN® enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and LEVAQUIN® use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if LEVAQUIN® is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding *[see Adverse Reactions (6.3)*; *Patient Counseling Information (17.4)]*.

7.3 Antidiabetic Agents

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with fluoroquinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered *[see Warnings and Precautions (5.11)*; *Adverse Reactions (6.2)*, *Patient Counseling Information (17.4)]*.

7.4 Non-Steroidal Anti-Inflammatory Drugs

The concomitant administration of a non-steroidal anti-inflammatory drug with a fluoroquinolone, including LEVAQUIN®, may increase the risk of CNS stimulation and convulsive seizures *[see Warnings and Precautions (5.6)]*.

7.5 Theophylline

No significant effect of LEVAQUIN® on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other fluoroquinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when LEVAQUIN® is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels *[see Warnings and Precautions (5.6)]*.

7.6 Cyclosporine

No significant effect of LEVAQUIN® on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other fluoroquinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and $t_{½}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for LEVAQUIN® or cyclosporine when administered concomitantly.

7.7 Digoxin

No significant effect of LEVAQUIN® on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for LEVAQUIN® or digoxin is required when administered concomitantly.

7.8 Probenecid and Cimetidine

No significant effect of probenecid or cimetidine on the C_{max} of levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and $t_{½}$ of levofloxacin were higher while CL/F and CL_R were lower during concomitant treatment of LEVAQUIN® with probenecid or

cimetidine compared to LEVAQUIN® alone. However, these changes do not warrant dosage adjustment for LEVAQUIN® when probenecid or cimetidine is co-administered.

7.9 Interactions with Laboratory or Diagnostic Testing

Some fluoroquinolones, including LEVAQUIN®, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

There are, however, no adequate and well-controlled studies in pregnant women. LEVAQUIN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Based on data on other fluoroquinolones and very limited data on LEVAQUIN®, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from LEVAQUIN® in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. *[see Warnings and Precautions (5.10) and Animal Toxicology and/or Pharmacology (13.2)]*.

Inhalational Anthrax (Post-Exposure)

Levofloxacin is indicated in pediatric patients for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate. The safety of levofloxacin in pediatric patients treated for more than 14 days has not been studied. The pharmacokinetics of levofloxacin following a single intravenous dose were investigated in pediatric patients ranging in age from six months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients resulting in lower plasma exposures than adults for a given mg/kg dose *[see Indications and Usage (1.13)*, *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3) and Clinical Studies (14.9)]*.

Adverse Events

In clinical trials, 1534 children (6 months to 16 years of age) were treated with oral and intravenous LEVAQUIN®. Children 6 months to 5 years of age received LEVAQUIN® 10 mg/kg twice a day and children greater than 5 years of age received 10 mg/kg once a day (maximum 500 mg per day) for approximately 10 days.

A subset of children in the clinical trials (1340 LEVAQUIN®-treated and 893 non-fluoroquinolone-treated) enrolled in a prospective, long-term surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendinopathy, gait abnormality) during 60 days and 1 year following the first dose of the study drug. Children treated with LEVAQUIN® had a significantly higher incidence of musculoskeletal disorders when compared to the non-fluoroquinolone-treated children as illustrated in Table 9.

Table 9: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

Follow-up Period	**LEVAQUIN® N = 1340**	**Non-Fluoroquinolone* N = 893**	**p-value†**
60 days	28 (2.1%)	8 (0.9%)	p = 0.038
1 year‡	46 (3.4%)	16 (1.8%)	p = 0.025

* Non-Fluoroquinolone: ceftriaxone, amoxicillin/ clavulanate, clarithromycin
† 2-sided Fisher's Exact Test
‡ There were 1199 LEVAQUIN®-treated and 804 non-fluoroquinolone-treated children who had a one-year evaluation visit. However, the incidence of musculoskeletal disorders was calculated using all reported events during the specified period for all children enrolled regardless of whether they completed the 1-year evaluation visit.

Arthralgia was the most frequently occurring musculoskeletal disorder in both treatment groups. Most of the musculoskeletal disorders in both groups involved multiple weight-bearing joints. Disorders were moderate in 8/46 (17%) children and mild in 35/46 (76%) LEVAQUIN®-treated children and most were treated with analgesics. The median time to resolution was 7 days for LEVAQUIN®-treated children and 9 for non-fluoroquinolone-treated

children (approximately 80% resolved within 2 months in both groups). No child had a severe or serious disorder and all musculoskeletal disorders resolved without sequelae.

Vomiting and diarrhea were the most frequently reported adverse events, occurring in similar frequency in the LEVAQUIN®-treated and non-fluoroquinolone-treated children.

In addition to the events reported in pediatric patients in clinical trials, events reported in adults during clinical trials or post-marketing experience *[see Adverse Reactions (6)]* may also be expected to occur in pediatric patients.

8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as LEVAQUIN®. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing LEVAQUIN® to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue LEVAQUIN® and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur *[see Boxed Warning*; *Warnings and Precautions (5.1); and Adverse Reactions (6.3)]*.

In phase 3 clinical trials, 1,945 LEVAQUIN®-treated patients (26%) were ≥ 65 years of age. Of these, 1,081 patients (14%) were between the ages of 65 and 74 and 864 patients (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Severe, and sometimes fatal, cases of hepatotoxicity have been reported post-marketing in association with LEVAQUIN®. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. LEVAQUIN® should be discontinued immediately if the patient develops signs and symptoms of hepatitis *[see Warnings and Precautions (5.5)]*.

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using LEVAQUIN® with concomitant drugs that can result in prolongation of the QT interval (e.g., Class IA or Class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia) *[see Warnings and Precautions (5.9)]*.

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However, since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance < 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of LEVAQUIN® are not required following hemodialysis or CAPD *[see Dosage and Administration (2.3)]*.

8.7 Hepatic Impairment

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

10 OVERDOSAGE

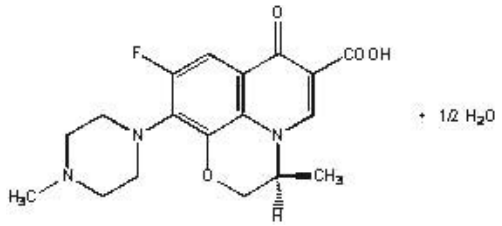
In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

LEVAQUIN® exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of LEVAQUIN®: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents.

11 DESCRIPTION

LEVAQUIN® is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

Figure 1: The Chemical Structure of Levofloxacin



The empirical formula is $C_{18}H_{20}FN_3O_4$ • ½ H_2O and the molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/mL). Levofloxacin is considered *soluble to freely soluble* in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL) and is considered *freely soluble* in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9.

Levofloxacin has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: $Al^{+3}>Cu^{+2}>Zn^{+2}>Mg^{+2}>Ca^{+2}$.

Excipients and Description of Dosage Forms

LEVAQUIN® Tablets

LEVAQUIN® Tablets are available as film-coated tablets and contain the following inactive ingredients:

- 250 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.
- 500 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red and yellow iron oxides.
- 750 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80.

LEVAQUIN® Oral Solution

LEVAQUIN® Oral Solution, 25 mg/mL, is a multi-use self-preserving aqueous solution of levofloxacin with pH ranging from 5.0 to 6.0. The appearance of LEVAQUIN® Oral Solution may range from clear yellow to clear greenish-yellow. This does not adversely affect product potency.

LEVAQUIN® Oral Solution contains the following inactive ingredients: sucrose, glycerin, sucralose, hydrochloric acid, purified water, propylene glycol, artificial and natural flavors, benzyl alcohol, ascorbic acid, and caramel color. It may also contain a solution of sodium hydroxide for pH adjustment.

LEVAQUIN® Injection

The appearance of LEVAQUIN® Injection may range from a clear yellow to a clear greenish-yellow solution. This does not adversely affect product potency.

LEVAQUIN® Injection in Single-Use Vials is a sterile, preservative-free aqueous solution of levofloxacin in Water for Injection, with pH ranging from 3.8 to 5.8.

LEVAQUIN® Injection Premix in Single-Use Flexible Containers is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. This is a dilute, non-pyrogenic, nearly isotonic premixed solution that contains levofloxacin in 5% Dextrose (D_5W). Solutions of hydrochloric acid and sodium hydroxide may have been added to adjust the pH.

The flexible container is fabricated from a specially formulated non-plasticized, thermoplastic copolyester (CR3). The amount of water that can permeate from the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the flexible container can leach out certain of the container's chemical components in very small amounts within the expiration period. The suitability of the container material has been confirmed by tests in animals according to USP biological tests for plastic containers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Levofloxacin is a member of the fluoroquinolone class of antibacterial agents *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

The mean ± SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral tablet, oral solution, or intravenous (IV) doses of LEVAQUIN® are summarized in Table 10.

Table 10: Mean ± SD Levofloxacin PK Parameters

Regimen	C_{max} (mcg/mL)	T_{max} (h)	AUC (mcg·h/mL)	CL/F[1] (mL/min)	Vd/F[2] (L)	$t_{1/2}$ (h)	CL_R (mL/min)
Single dose							
250 mg oral tablet[3]	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	ND	7.3 ± 0.9	142 ± 21
500 mg oral tablet[3]*	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	ND	6.3 ± 0.6	103 ± 30
500 mg oral solution[12]	5.8 ± 1.8	0.8 ± 0.7	47.8 ± 10.8	183 ± 40	112 ± 37.2	7.0 ± 1.4	ND
500 mg IV[3]	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.4	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
750 mg oral tablet[5]*	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	129 ± 24	83 ± 17	7.5 ± 0.9	ND
750 mg IV[5]	11.5 ± 4.0[4]	ND	110 ± 40	126 ± 39	75 ± 13	7.5 ± 1.6	ND
Multiple dose							
500 mg every 24h oral tablet[3]	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg every 24h IV[3]	6.4 ± 0.8	ND	54.6 ± 11.1	158 ± 29	91 ± 12	7.0 ± 0.8	99 ± 28
500 mg or 250 mg every 24h IV, patients with bacterial infection[6]	8.7± 4.0[7]	ND	72.5 ± 51.2[7]	154 ± 72	111 ± 58	ND	ND
750 mg every 24h oral tablet[5]	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
750 mg every 24h IV[5]	12.1 ± 4.1[4]	ND	108 ± 34	126 ± 37	80 ± 27	7.9 ± 1.9	ND
500 mg oral tablet single dose, effects of gender and age:							
Male[8]	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38
Female[9]	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40
Young[10]	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6.0 ± 0.9	140 ± 33
Elderly[11]	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2.0	91 ± 29
500 mg oral single dose tablet, patients with renal insufficiency:							
CLCR 50–80 mL/min	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8	88 ± 10	ND	9.1 ± 0.9	57 ± 8
CLCR 20–49 mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	51 ± 19	ND	27 ± 10	26 ± 13
CLCR <20 mL/min	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5	33 ± 8	ND	35 ± 5	13 ± 3
Hemodialysis	5.7 ± 1.0	2.8 ± 2.2	ND	ND	ND	76 ± 42	ND
CAPD	6.9 ± 2.3	1.4 ± 1.1	ND	ND	ND	51 ± 24	ND

[1] clearance/bioavailability
[2] volume of distribution/bioavailability
[3] healthy males 18–53 years of age
[4] 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose
[5] healthy male and female subjects 18–54 years of age
[6] 500 mg every 48h for patients with moderate renal impairment (CLCR 20–50 mL/min) and infections of the respiratory tract or skin
[7] dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling
[8] healthy males 22–75 years of age
[9] healthy females 18–80 years of age
[10] young healthy male and female subjects 18–36 years of age
[11] healthy elderly male and female subjects 66–80 years of age
[12] healthy males and females 19–55 years of age.

*Absolute bioavailability; F=0.99 ± 0.08 from a 500 mg tablet and F=0.99 ± 0.06 from a 750 mg tablet;
ND=not determined.

Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of levofloxacin from a 500 mg tablet and a 750 mg tablet of LEVAQUIN® are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of LEVAQUIN® to healthy volunteers, the mean ± SD peak plasma concentration attained was 6.2 ± 1.0 mcg/mL after a 500 mg dose infused over 60 minutes and 11.5 ± 4.0 mcg/mL after a 750 mg dose infused over 90 minutes. LEVAQUIN® Oral Solution and Tablet formulations are bioequivalent.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ± SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ± 1.4 and 0.5 ± 0.2 mcg/mL after the 500 mg doses, and 8.6 ± 1.9 and 1.1 ± 0.4 mcg/mL after the 750 mg doses, respectively. The mean ± SD peak and trough plasma concentrations attained following multiple once-daily IV regimens were approximately 6.4 ± 0.8 and 0.6 ± 0.2 mcg/mL after the 500 mg doses, and 12.1 ± 4.1 and 1.3 ± 0.71 mcg/mL after the 750 mg doses, respectively. Oral administration of a 500 mg dose of LEVAQUIN® with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following tablet and approximately 25% following oral solution administration. Therefore, LEVAQUIN® Tablets can be administered without regard to food. It is recommended that LEVAQUIN® Oral Solution be taken 1 hour before or 2 hours after eating.

The plasma concentration profile of levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for LEVAQUIN® Tablets when equal doses (mg/mg) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable *(see Figure 2 and Figure 3)*.

Figure 2: Mean Levofloxacin Plasma Concentration vs. Time Profile: 750 mg

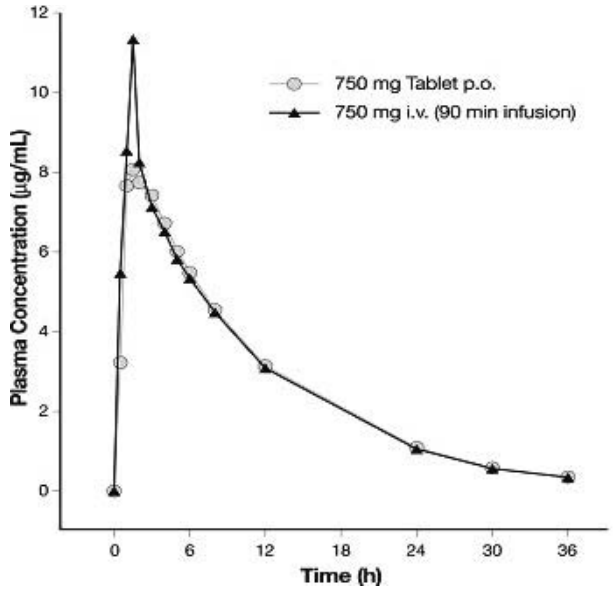
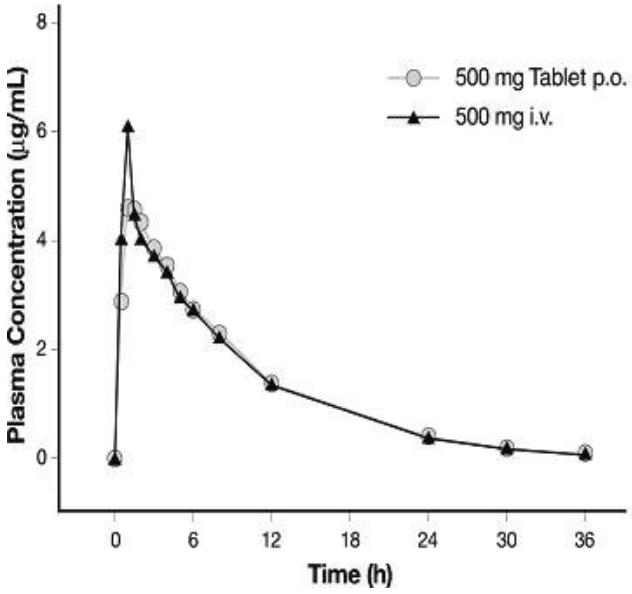


Figure 3: Mean Levofloxacin Plasma Concentration vs. Time Profile: 500 mg



Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at

approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750 mg and 500 mg doses of LEVAQUIN®, respectively, to healthy subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5-fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 mcg/g over a 24-hour period after a single 500 mg oral dose.

In vitro, over a clinically relevant range (1 to 10 mcg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity.

Excretion

Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving LEVAQUIN®.

Geriatric

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of LEVAQUIN® to healthy elderly subjects (66 – 80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. LEVAQUIN® dose adjustment based on age alone is not necessary *[see Use in Specific Populations (8.5)]*.

Pediatrics

The pharmacokinetics of levofloxacin following a single 7 mg/kg intravenous dose were investigated in pediatric patients ranging in age from 6 months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients, resulting in lower plasma exposures than adults for a given mg/kg dose. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 8 mg/kg every 12 hours (not to exceed 250 mg per dose) for pediatric patients 6 months to 17 years of age would achieve comparable steady state plasma exposures (AUC_{0-24} and C_{max}) to those observed in adult patients administered 500 mg of levofloxacin once every 24 hours.

Gender

There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of LEVAQUIN® to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race

The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 non-white. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal Impairment

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in adult patients with impaired renal function (creatinine clearance < 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of LEVAQUIN® are not required following hemodialysis or CAPD *[see Dosage and Administration (2.3)*, *Use in Specific Populations (8.6)]*.

Hepatic Impairment

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment *[see Use in Specific Populations (8.7)]*.

Bacterial Infection

The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

Drug-Drug Interactions

The potential for pharmacokinetic drug interactions between LEVAQUIN® and antacids, warfarin, theophylline, cyclosporine, digoxin, probenecid, and cimetidine has been evaluated *[see Drug Interactions (7)]*.

12.4 Microbiology

Mechanism of Action

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Drug Resistance

Fluoroquinolone resistance can arise through mutations in defined regions of DNA gyrase or topoisomerase IV, termed the Quinolone-Resistance Determining Regions (QRDRs), or through altered efflux.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Activity *in vitro* and *in vivo*

Levofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms.

Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in *Indications and Usage (1)*:

Aerobic Gram-Positive Microorganisms

Enterococcus faecalis (many strains are only moderately susceptible)

Staphylococcus aureus (methicillin-susceptible strains)

Staphylococcus epidermidis (methicillin-susceptible strains)

Staphylococcus saprophyticus

Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP][1])

Streptococcus pyogenes

[1] MDRSP (Multi-drug resistant *Streptococcus pneumoniae*) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime; macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Aerobic Gram-Negative Microorganisms

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Legionella pneumophila

Moraxella catarrhalis

Proteus mirabilis

Pseudomonas aeruginosa[2]

Serratia marcescens

[2] As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with LEVAQUIN®.

Other Microorganisms

Chlamydophila pneumoniae

Mycoplasma pneumoniae

Levofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of plasma levels as a surrogate marker in a rhesus monkey model for anthrax (post-exposure) *[see Indications and Usage (1.13), Clinical Studies (14.9)]*.

The following *in vitro* data are available, but their clinical significance is unknown: Levofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 2 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of LEVAQUIN® in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms

Staphylococcus haemolyticus

β-hemolytic *Streptococcus (Group C/F)*

β-hemolytic *Streptococcus (Group G)*

Streptococcus agalactiae

Streptococcus milleri

Viridans group *streptococci*

Aerobic Gram-Negative Microorganisms

Acinetobacter baumannii

Acinetobacter lwoffii

Bordetella pertussis

Citrobacter koseri

Citrobacter freundii

Enterobacter aerogenes

Enterobacter sakazakii

Klebsiella oxytoca

Morganella morganii

Pantoea agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas fluorescens

Anaerobic Gram-Positive Microorganisms

Clostridium perfringens

Susceptibility Tests

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity.

- **Dilution techniques:**

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the criteria outlined in Table 11.

- **Diffusion techniques**:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg levofloxacin to test the susceptibility of microorganisms to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg levofloxacin disk should be interpreted according to the criteria outlined in Table 11. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

Table 11: Susceptibility Interpretive Criteria for LEVAQUIN®

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤2	4	≥8	≥17	14–16	≤13
Enterococcus faecalis	≤2	4	≥8	≥17	14–16	≤13
Methicillin-susceptible *Staphylococcus* species	≤2	4	≥8	≥17	14–16	≤13
Pseudomonas aeruginosa	≤2	4	≥8	≥17	14–16	≤13
Haemophilus influenzae	≤2[*]	--[†]	--[†]	≥17[‡]	--[†]	--[†]
Haemophilus parainfluenzae	≤2[*]	--[†]	--[†]	≥17[‡]	--[†]	--[†]
Streptococcus pneumoniae	≤2[§]	4[§]	≥8[§]	≥17[¶]	14–16[¶]	≤13[¶]
Streptococcus pyogenes	≤2	4	≥8	≥17	14–16	≤13

S = Susceptible, I = Intermediate, R = Resistant

[*] These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[1]

[†] The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC /zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

[‡] These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[2]

[§] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2–5% lysed horse blood.

[¶] These zone diameter standards for *Streptococcus* spp. including *S. pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

A report of *Susceptible* indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of *Intermediate* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

- **Quality Control**:

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For dilution technique, standard levofloxacin powder should give the MIC values provided in Table 12. For diffusion technique, the 5 mcg levofloxacin disk should provide zone diameters provided in Table 12.

Table 12: Quality Control for Susceptibility Testing

Microorganism	Microorganism QC Number	MIC (mcg/mL)	Disk Diffusion (zone diameter in mm)
Enterococcus faecalis	ATCC 29212	0.25 – 2	--
Escherichia coli	ATCC 25922	0.008 – 0.06	29 – 37
*Escherichia coli***	ATCC 35218	0.015 – 0.06	--
Haemophilus influenzae	ATCC 49247	0.008 – 0.03*	32 – 40†
Pseudomonas aeruginosa	ATCC 27853	0.5 – 4	19 – 26
Staphylococcus aureus	ATCC 29213	0.06 – 0.5	--
Staphylococcus aureus	ATCC 25923	--	25 – 30
Streptococcus pneumoniae	ATCC 49619	0.5 – 2‡	20 – 25§

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).[1]
† This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM).[2]
‡ This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2–5% lysed horse blood.
§ This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.
** Careful maintenance of this organism is required as the strain may lose its plasmid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day*)* was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 mcg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of LEVAQUIN® averaged approximately 11.8 mcg/g at C_{max}.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day,

corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

13.2 Animal Toxicology and/or Pharmacology

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested *[see Warnings and Precautions (5.10)]*. In immature dogs (4–5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with levofloxacin at 40 mg/kg/day exhibited clinically severe arthrotoxicity resulting in the termination of dosing at Day 8 of a 14-day dosing routine. Slight musculoskeletal clinical effects, in the absence of gross pathological or histopathological effects, resulted from the lowest dose level of 2.5 mg/kg/day (approximately 0.2-fold the pediatric dose based upon AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (approximately 0.7-fold and 2.4-fold the pediatric dose, respectively, based on AUC comparisons). Articular cartilage gross pathology and histopathology persisted to the end of the 18-week recovery period for those dogs from the 10 and 40 mg/kg/day dose levels.

When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other quinolones.

While crystalluria has been observed in some intravenous rat studies, urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs.

In dogs, levofloxacin administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.

In vitro and *in vivo* studies in animals indicate that levofloxacin is neither an enzyme inducer nor inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

14 CLINICAL STUDIES

14.1 Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multicenter, randomized, open-label study comparing intravenous LEVAQUIN®

(750 mg once daily) followed by oral LEVAQUIN® (750 mg once daily) for a total of 7–15 days to intravenous imipenem/cilastatin (500–1000 mg every 6–8 hours daily) followed by oral ciprofloxacin (750 mg every 12 hours daily) for a total of 7–15 days. LEVAQUIN®-treated patients received an average of 7 days of intravenous therapy (range: 1–16 days); comparator-treated patients received an average of 8 days of intravenous therapy (range: 1–19 days).

Overall, in the clinically and microbiologically evaluable population, adjunctive therapy was empirically initiated at study entry in 56 of 93 (60.2%) patients in the LEVAQUIN® arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the LEVAQUIN® arm and 7 days in the comparator. In clinically and microbiologically evaluable patients with documented *Pseudomonas aeruginosa* infection, 15 of 17 (88.2%) received ceftazidime (N=11) or piperacillin/tazobactam (N=4) in the LEVAQUIN® arm and 16 of 17 (94.1%) received an aminoglycoside in the comparator arm. Overall, in clinically and microbiologically evaluable patients, vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the LEVAQUIN® arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin-resistant *S. aureus* infection.

Clinical success rates in clinically and microbiologically evaluable patients at the posttherapy visit (primary study endpoint assessed on day 3–15 after completing therapy) were 58.1% for LEVAQUIN® and 60.6% for comparator. The 95% CI for the difference of response rates (LEVAQUIN® minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the posttherapy visit were 66.7% for LEVAQUIN® and 60.6% for comparator. The 95% CI for the difference of eradication rates (LEVAQUIN® minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen are detailed in Table 13.

Table 13: Clinical Success Rates and Microbiological Eradication Rates (Nosocomial Pneumonia)

Pathogen	N	LEVAQUIN® No. (%) of Patients Microbiologic/ Clinical Outcomes	N	Imipenem/Cilastatin No. (%) of Patients Microbiologic/ Clinical Outcomes
MSSA*	21	14 (66.7)/13 (61.9)	19	13 (68.4)/15 (78.9)
P. aeruginosa†	17	10 (58.8)/11 (64.7)	17	5 (29.4)/7 (41.2)
S. marcescens	11	9 (81.8)/7 (63.6)	7	2 (28.6)/3 (42.9)
E. coli	12	10 (83.3)/7 (58.3)	11	7 (63.6)/8 (72.7)
K. pneumoniae‡	11	9 (81.8)/5 (45.5)	7	6 (85.7)/3 (42.9)
H. influenzae	16	13 (81.3)/10 (62.5)	15	14 (93.3)/11 (73.3)
S. pneumoniae	4	3 (75.0)/3 (75.0)	7	5 (71.4)/4 (57.1)

* Methicillin-susceptible *S. aureus*
† See above text for use of combination therapy
‡ The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study

14.2 Community-Acquired Pneumonia: 7–14 day Treatment Regimen

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in 2 pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing LEVAQUIN® 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with LEVAQUIN® at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (LEVAQUIN® minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg LEVAQUIN® administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies are presented in Table 14.

Table 14: Microbiologic Eradication Rates Across 2 Community Acquired Pneumonia Clinical Studies

Pathogen	No. Pathogens	Microbiologic Eradication Rate (%)
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100.0

Community-Acquired Pneumonia Due to Multi-Drug Resistant *Streptococcus pneumoniae*

LEVAQUIN® was effective for the treatment of community-acquired pneumonia caused by multi-drug resistant *Streptococcus pneumoniae* (MDRSP). MDRSP isolates are strains resistant to two or more of the following antibacterials: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins (e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole). Of 40 microbiologically evaluable patients with MDRSP isolates, 38 patients (95.0%) achieved clinical and bacteriologic success at post-therapy. The clinical and bacterial success rates are shown in Table 15.

Table 15: Clinical and Bacterial Success Rates for LEVAQUIN®-Treated MDRSP in Community Acquired Pneumonia Patients (Population Valid for Efficacy)

Screening Susceptibility	Clinical Success		Bacteriological Success*	
	n/N†	%	n/N‡	%
Penicillin-resistant	16/17	94.1	16/17	94.1
2nd generation Cephalosporin resistant	31/32	96.9	31/32	96.9
Macrolide-resistant	28/29	96.6	28/29	96.6
Trimethoprim/ Sulfamethoxazole resistant	17/19	89.5	17/19	89.5
Tetracycline-resistant	12/12	100	12/12	100

* One patient had a respiratory isolate that was resistant to tetracycline, cefuroxime, macrolides and TMP/SMX and intermediate to penicillin and a blood isolate that was intermediate to penicillin and cefuroxime and resistant to the other classes. The patient is included in the database based on respiratory isolate.

† n=the number of microbiologically evaluable patients who were clinical successes; N=number of microbiologically evaluable patients in the designated resistance group.

‡ n=the number of MDRSP isolates eradicated or presumed eradicated in microbiologically evaluable patients; N=number of MDRSP isolates in a designated resistance group.

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in Table 16.

Table 16: Clinical Success and Bacteriologic Eradication Rates for Resistant *Streptococcus pneumoniae* (Community Acquired Pneumonia)

Type of Resistance	Clinical Success	Bacteriologic Eradication
Resistant to 2 antibacterials	17/18 (94.4%)	17/18 (94.4%)
Resistant to 3 antibacterials	14/15 (93.3%)	14/15 (93.3%)
Resistant to 4 antibacterials	7/7 (100%)	7/7 (100%)
Resistant to 5 antibacterials	0	0
Bacteremia with MDRSP	8/9 (89%)	8/9 (89%)

14.3 Community-Acquired Pneumonia: 5-Day Treatment Regimen

To evaluate the safety and efficacy of the higher dose and shorter course of LEVAQUIN®, 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multicenter study comparing LEVAQUIN® 750 mg, IV or orally, every day for five days or LEVAQUIN® 500 mg IV or orally, every day for 10 days.

Clinical success rates (cure plus improvement) in the clinically evaluable population were 90.9% in the LEVAQUIN® 750 mg group and 91.1% in the LEVAQUIN® 500 mg group. The 95% CI for the difference of response rates (LEVAQUIN® 750 minus LEVAQUIN® 500) was [-5.9, 5.4]. In the clinically evaluable population (31–38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the LEVAQUIN® 750 mg group and 2 out of 147 patients in the LEVAQUIN® 500 mg group. Given the small numbers observed, the significance of this

finding cannot be determined statistically. The microbiological efficacy of the 5-day regimen was documented for infections listed in Table 17.

Table 17: Microbiological Eradication Rates (Community-Acquired Pneumonia)

Penicillin susceptible *S. pneumoniae*	19/20
Haemophilus influenzae	12/12
Haemophilus parainfluenzae	10/10
Mycoplasma pneumoniae	26/27
Chlamydophila pneumoniae	13/15

14.4 Acute Bacterial Sinusitis: 5-day and 10–14 day Treatment Regimens

LEVAQUIN® is approved for the treatment of acute bacterial sinusitis (ABS) using either 750 mg by mouth × 5 days or 500 mg by mouth once daily × 10–14 days. To evaluate the safety and efficacy of a high dose short course of LEVAQUIN®, 780 outpatient adults with clinically and radiologically determined acute bacterial sinusitis were evaluated in a double-blind, randomized, prospective, multicenter study comparing LEVAQUIN® 750 mg by mouth once daily for five days to LEVAQUIN® 500 mg by mouth once daily for 10 days.

Clinical success rates (defined as complete or partial resolution of the pre-treatment signs and symptoms of ABS to such an extent that no further antibiotic treatment was deemed necessary) in the microbiologically evaluable population were 91.4% (139/152) in the LEVAQUIN® 750 mg group and 88.6% (132/149) in the LEVAQUIN® 500 mg group at the test-of-cure (TOC) visit (95% CI [-4.2, 10.0] for LEVAQUIN® 750 mg minus LEVAQUIN® 500 mg).

Rates of clinical success by pathogen in the microbiologically evaluable population who had specimens obtained by antral tap at study entry showed comparable results for the five- and ten-day regimens at the test-of-cure visit 22 days post treatment.

Table 18: Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture (Acute Bacterial Sinusitis)

Pathogen	LEVAQUIN® 750 mg × 5 days	LEVAQUIN® 500 mg × 10 days
*Streptococcus pneumoniae**	25/27 (92.6%)	26/27 (96.3%)
*Haemophilus influenzae**	19/21 (90.5%)	25/27 (92.6%)
*Moraxella catarrhalis**	10/11 (90.9%)	13/13 (100%)

* Note: Forty percent of the subjects in this trial had specimens obtained by sinus endoscopy. The efficacy data for subjects whose specimen was obtained endoscopically were comparable to those presented in the above table.

14.5 Complicated Skin and Skin Structure Infections

Three hundred ninety-nine patients were enrolled in an open-label, randomized, comparative study for complicated skin and skin structure infections. The patients were randomized to

receive either LEVAQUIN® 750 mg once daily (IV followed by oral), or an approved comparator for a median of 10 ± 4.7 days. As is expected in complicated skin and skin structure infections, surgical procedures were performed in the LEVAQUIN® and comparator groups. Surgery (incision and drainage or debridement) was performed on 45% of the LEVAQUIN®-treated patients and 44% of the comparator-treated patients, either shortly before or during antibiotic treatment and formed an integral part of therapy for this indication.

Among those who could be evaluated clinically 2–5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with LEVAQUIN® and 106/132 (80.3%) for patients treated with the comparator.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

14.6 Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB_3) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral LEVAQUIN® 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 and 125 microbiologically evaluable patients were enrolled in the LEVAQUIN® and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5–18 days after completion of therapy was 75.0% in the LEVAQUIN® group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for LEVAQUIN® minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented in Table 19.

Table 19: Microbiological Eradication Rates (Chronic Bacterial Prostatitis)

	LEVAQUIN® (N=136)		**Ciprofloxacin (N=125)**	
Pathogen	N	Eradication	N	Eradication
E. coli	15	14 (93.3%)	11	9 (81.8%)
E. faecalis	54	39 (72.2%)	44	33 (75.0%)
*S. epidermidis**	11	9 (81.8%)	14	11 (78.6%)

* Eradication rates shown are for patients who had a sole pathogen only; mixed cultures were excluded.

Eradication rates for *S. epidermidis* when found with other co-pathogens are consistent with rates seen in pure isolates.

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5–18 days after completion of therapy were 75.0% for LEVAQUIN®-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for LEVAQUIN® minus ciprofloxacin). Clinical long-term success (24–45 days after completion of therapy) rates were 66.7% for the LEVAQUIN®-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for LEVAQUIN® minus ciprofloxacin).

14.7 Complicated Urinary Tract Infections and Acute Pyelonephritis: 5-day Treatment Regimen

To evaluate the safety and efficacy of the higher dose and shorter course of LEVAQUIN®, 1109 patients with cUTI and AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from November 2004 to April 2006 comparing LEVAQUIN® 750 mg IV or orally once daily for 5 days (546 patients) with ciprofloxacin 400 mg IV or 500 mg orally twice daily for 10 days (563 patients). Patients with AP complicated by underlying renal diseases or conditions such as complete obstruction, surgery, transplantation, concurrent infection or congenital malformation were excluded. Efficacy was measured by bacteriologic eradication of the baseline organism(s) at the post-therapy visit in patients with a pathogen identified at baseline. The post-therapy (test-of-cure) visit occurred 10 to 14 days after the last active dose of LEVAQUIN® and 5 to 9 days after the last dose of active ciprofloxacin.

The bacteriologic cure rates overall for LEVAQUIN® and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 20.

Table 20: Bacteriologic Eradication at Test-of-Cure

	LEVAQUIN® 750 mg orally or IV once daily for 5 days		**Ciprofloxacin** 400 mg IV/500 mg orally twice daily for 10 days		**Overall Difference [95% CI]**
	n/N	%	n/N	%	LEVAQUIN®-Ciprofloxacin
mITT Population*					
Overall (cUTI or AP)	252/333	75.7	239/318	75.2	0.5 (-6.1, 7.1)
cUTI	168/230	73.0	157/213	73.7	
AP	84/103	81.6	82/105	78.1	
Microbiologically Evaluable Population†					
Overall (cUTI or AP)	228/265	86.0	215/241	89.2	-3.2 [-8.9, 2.5]
cUTI	154/185	83.2	144/165	87.3	
AP	74/80	92.5	71/76	93.4	

* The mITT population included patients who received study medication and who had a positive ($\geq 10^5$ CFU/mL) urine culture with no more than 2 uropathogens at baseline. Patients with missing response were counted as failures in this analysis.

† The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present at $\geq 10^5$ CFU/mL, a valid test-of-cure urine culture, no pathogen isolated from blood resistant to study drug, no premature discontinuation or loss to follow-up, and compliance with treatment (among other criteria).

Microbiologic eradication rates in the Microbiologically Evaluable population at TOC for individual pathogens recovered from patients randomized to LEVAQUIN® treatment are presented in Table 21.

Table 21: Microbiological Eradication Rates for Individual Pathogens Recovered From Patients Randomized to LEVAQUIN® 750 mg QD for 5 Days Treatment

Pathogen	**Microbiologic Eradication Rate (n/N)**	**%**
*Escherichia coli**	155/172	90
Klebsiella pneumoniae	20/23	87
Proteus mirabilis	12/12	100

* The predominant organism isolated from patients with AP was *E. coli*: 91% (63/69) eradication in AP and 89% (92/103) in patients with cUTI.

14.8 Complicated Urinary Tract Infections and Acute Pyelonephritis: 10-day Treatment Regimen

To evaluate the safety and efficacy of the 250 mg dose, 10 day regimen of LEVAQUIN®, 567 patients with uncomplicated UTI, mild-to-moderate cUTI, and mild-to-moderate AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from June 1993 to January 1995 comparing LEVAQUIN® 250 mg orally once daily for 10 days (285 patients) with ciprofloxacin 500 mg orally twice daily for 10 days (282 patients). Patients

with a resistant pathogen, recurrent UTI, women over age 55 years, and with an indwelling catheter were initially excluded, prior to protocol amendment which took place after 30% of enrollment. Microbiological efficacy was measured by bacteriologic eradication of the baseline organism(s) at 1–12 days post-therapy in patients with a pathogen identified at baseline.

The bacteriologic cure rates overall for LEVAQUIN® and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 22.

Table 22: Bacteriologic Eradication Overall (cUTI or AP) at Test-Of-Cure*

	LEVAQUIN® 250 mg once daily for 10 days		**Ciprofloxacin** 500 mg twice daily for 10 days	
	n/N	%	n/N	%
mITT Population†	174/209	83.3	184/219	84.0
Microbiologically Evaluable Population‡	164/177	92.7	159/171	93.0

* 1–9 days posttherapy for 30% of subjects enrolled prior to a protocol amendment; 5–12 days posttherapy for 70% of subjects.
† The mITT population included patients who had a pathogen isolated at baseline. Patients with missing response were counted as failures in this analysis.
‡ The Microbiologically Evaluable population included mITT patients who met protocol-specified evaluability criteria.

14.9 Inhalational Anthrax (Post-Exposure)

The effectiveness of LEVAQUIN® for this indication is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. LEVAQUIN® has not been tested in humans for the post-exposure prevention of inhalation anthrax. The mean plasma concentrations of LEVAQUIN® associated with a statistically significant improvement in survival over placebo in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens *[see Indications and Usage (1.13)*; *Dosage and Administration (2.1*, *2.2)]*.

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_{0-24}) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily *[see Clinical Pharmacology (12.3)]*.

In adults, the safety of LEVAQUIN® for treatment durations of up to 28 days is well characterized. However, information pertaining to extended use at 500 mg daily up to 60 days is limited. Prolonged LEVAQUIN® therapy in adults should only be used when the benefit outweighs the risk.

In pediatric patients, the safety of levofloxacin for treatment durations of more than 14 days has not been studied. An increased incidence of musculoskeletal adverse events (arthralgia, arthritis, tendinopathy, gait abnormality) compared to controls has been observed in clinical studies with treatment duration of up to 14 days. Long-term safety data, including effects on cartilage, following the administration of levofloxacin to pediatric patients is limited *[see Warnings and Precautions (5.10)*, *Use in Specific Populations (8.4)]*.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD_{50} (~2.7×10^6) spores (range 17 – 118 LD_{50}) of *B. anthracis* (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 2.79 to 4.87 mcg/mL. Steady state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/mL. Mean (SD) steady state AUC_{0-24} was 33.4 ± 3.2 mcg.h/mL (range 30.4 to 36.0 mcg.h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral LEVAQUIN® beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10) [P=0.0011, 2-sided Fisher's Exact Test]. The one levofloxacin treated animal that died of anthrax did so following the 30-day drug administration period.

15 REFERENCES

1. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Approved Standard – Eighth Edition. Clinical and Laboratory Standards Institute document M7-A8, Vol. 29, No. 2, CLSI, Wayne, PA, January 2009.

2. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Disk Susceptibility Tests. Approved Standard – Tenth Edition. Clinical and Laboratory Standards Institute document M2-A10, Vol. 29, No. 1, CLSI, Wayne, PA, January 2009.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 LEVAQUIN® Tablets

LEVAQUIN® Tablets are supplied as 250, 500, and 750 mg capsule-shaped, coated tablets. LEVAQUIN® Tablets are packaged in bottles and in unit-dose blister strips in the following configurations:

- 250 mg tablets are terra cotta pink and are imprinted: "LEVAQUIN" on one side and "250" on the other side.
  - bottles of 50 (NDC 50458-920-50)
  - unit-dose/100 tablets (NDC 50458-920-10)
- 500 mg tablets are peach and are imprinted: "LEVAQUIN" on one side and "500" on the other side
  - bottles of 50 (NDC 50458-925-50)
  - unit-dose/100 tablets (NDC 50458-925-10)
- 750 mg tablets are white and are imprinted "LEVAQUIN" on one side and "750" on the other side
  - bottles of 20 (NDC 50458-930-20)
  - unit-dose/100 tablets (NDC 50458-930-10)

LEVAQUIN® Tablets should be stored at 15° to 30°C (59° to 86°F) in well-closed containers.

LEVAQUIN® Tablets are manufactured for Janssen Pharmaceuticals, Inc., Titusville, NJ 08560 by Janssen Ortho LLC, Gurabo, Puerto Rico 00778.

16.2 LEVAQUIN® Oral Solution

LEVAQUIN® Oral Solution is supplied in a 16 oz. multi-use bottle (NDC 50458-170-01). Each bottle contains 480 mL of the 25 mg/mL levofloxacin oral solution.

LEVAQUIN® Oral Solution should be stored at 25°C (77°F); excursions permitted to 15° – 30°C (59° to 86°F) [refer to USP controlled room temperature].

LEVAQUIN® Oral Solution is manufactured for Janssen Pharmaceuticals, Inc., Titusville, NJ 08560 by Janssen Pharmaceutica N.V., Beerse, Belgium.

16.3 LEVAQUIN® Injection, Single-Use Vials

LEVAQUIN® Injection is supplied in single-use vials. Each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 mL vials and 750 mg of levofloxacin in 30 mL vials.

- 25 mg/mL, 20 mL vials (NDC 50458-164-20)
- 25 mg/mL, 30 mL vials (NDC 50458-165-30)

LEVAQUIN® Injection in Single-Use Vials should be stored at controlled room temperature and protected from light.

LEVAQUIN® Injection in Single-Use Vials is manufactured for Janssen Pharmaceuticals, Inc., Titusville, NJ 08560 by Janssen Pharmaceutica N.V., Beerse, Belgium.

16.4 LEVAQUIN® Injection Pre-Mixed Solution, Single-Use in Flexible Container

LEVAQUIN® (levofloxacin in 5% dextrose) Injection is supplied as a single-use, premixed solution in flexible containers. Each bag contains a dilute solution with the equivalent of 250, 500, or 750 mg of levofloxacin, respectively, in 5% Dextrose (D5W).

- 5 mg/mL (250 mg), 100 mL flexible container, 50 mL fill (NDC 50458-167-01)
- 5 mg/mL (500 mg), 100 mL flexible container, 100 mL fill (NDC 50458-168-01)
- 5 mg/mL (750 mg), 150 mL flexible container, 150 mL fill (NDC 50458-166-01)

LEVAQUIN® Injection Premix in Flexible Containers should be stored at or below 25°C (77°F); however, brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat and protect from freezing and light. LEVAQUIN® Injection Premix in Flexible Containers is manufactured for Janssen Pharmaceuticals, Inc., Titusville, NJ 08560 by Hospira, Inc., Austin, TX 78728.

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Medication Guide (17.5)*

17.1 Antibacterial Resistance

Antibacterial drugs including LEVAQUIN® should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When LEVAQUIN® is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by LEVAQUIN® or other antibacterial drugs in the future.

17.2 Administration with Food, Fluids, and Concomitant Medications

Patients should be informed that LEVAQUIN® Tablets may be taken with or without food. LEVAQUIN® Oral Solution should be taken 1 hour before or 2 hours after eating. The tablet and oral solution should be taken at the same time each day.

Patients should drink fluids liberally while taking LEVAQUIN® to avoid formation of a highly concentrated urine and crystal formation in the urine.

Antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine should be taken at least two hours before or two hours after oral LEVAQUIN® administration.

17.3 Serious and Potentially Serious Adverse Reactions

Patients should be informed of the following serious adverse reactions that have been associated with LEVAQUIN® or other fluoroquinolone use:

- **Tendon Disorders**: Patients should contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue LEVAQUIN® treatment. **The risk of severe tendon disorders with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants**.
- **Exacerbation of Myasthenia Gravis:** Patients should inform their physician of any history of myasthenia gravis. Patients should notify their physician if they experience any symptoms of muscle weakness, including respiratory difficulties.
- **Hypersensitivity Reactions**: Patients should be informed that LEVAQUIN® can cause hypersensitivity reactions, even following the first dose. Patients should discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.
- **Hepatotoxicity**: Severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking LEVAQUIN®. Patients should inform their physician and be instructed to discontinue LEVAQUIN® treatment immediately if they experience any signs or symptoms of liver injury including: loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine.
- **Convulsions**: Convulsions have been reported in patients taking fluoroquinolones, including LEVAQUIN®. Patients should notify their physician before taking this drug if they have a history of convulsions.
- **Neurologic Adverse Effects (e.g., dizziness, lightheadedness, increased intracranial pressure)**: Patients should know how they react to LEVAQUIN® before they operate an

automobile or machinery or engage in other activities requiring mental alertness and coordination. Patients should notify their physician if persistent headache with or without blurred vision occurs.

- **Diarrhea**: Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.
- **Peripheral Neuropathies**: If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should discontinue treatment and contact their physician.
- **Prolongation of the QT Interval**: Patients should inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Patients should notify their physicians if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.
- **Musculoskeletal Disorders in Pediatric Patients:** Parents should inform their child's physician if their child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any tendon or joint-related problems that occur during or following LEVAQUIN® therapy *[see Warnings and Precautions (5.10)* and *Use in Specific Populations (8.4)]*.
- **Photosensitivity/Phototoxicity**: Patients should be advised that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolone antibiotics. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking fluoroquinolones. If patients need to be outdoors when taking fluoroquinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn like reaction or skin eruption occurs, patients should contact their physician.

17.4 Drug Interactions with Insulin, Oral Hypoglycemic Agents, and Warfarin

Patients should be informed that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue LEVAQUIN® and consult a physician.

Patients should be informed that concurrent administration of warfarin and LEVAQUIN® has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin, be monitored for evidence of bleeding, and also have their anticoagulation tests closely monitored while taking warfarin concomitantly.

Active Ingredient Made in Japan

Finished Product Manufactured by:

- Janssen Ortho LLC, Gurabo, Puerto Rico 00778 (for the Tablets).
- Janssen Pharmaceutica N.V., Beerse, Belgium (for the Oral Solution and Injection, Single-Use Vials).
- Hospira, Inc., Austin, TX 78728 (for the Injection Pre-Mixed Solution Single-Use in Flexible Container).

Manufactured for:

- Janssen Pharmaceuticals, Inc., Titusville, NJ 08560.

Issued October 2011.

17.5 FDA-Approved Medication Guide

MEDICATION GUIDE
LEVAQUIN® [Leave ah kwin]
(levofloxacin)
250 mg Tablets, 500 mg Tablets, and 750 mg Tablets
And
LEVAQUIN® (levofloxacin) Oral Solution, 25 mg/mL
And
LEVAQUIN® (levofloxacin) Injection, for Intravenous Use
And
LEVAQUIN® (levofloxacin in 5% dextrose) Injection, for Intravenous Use

Read the Medication Guide that comes with LEVAQUIN® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about LEVAQUIN®?

LEVAQUIN® belongs to a class of antibiotics called fluoroquinolones. LEVAQUIN® can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take LEVAQUIN®.

1. Tendon rupture or swelling of the tendon (tendinitis).

- **Tendon problems can happen in people of all ages who take LEVAQUIN®.** Tendons are tough cords of tissue that connect muscles to bones.
    - Some tendon problems include pain, swelling, tears, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites.
- **The risk of getting tendon problems while you take LEVAQUIN® is higher if you**:
    - are over 60 years of age
    - are taking steroids (corticosteroids)
    - have had a kidney, heart or lung transplant.
- **Tendon problems can happen in people who do not have the above risk factors when they take LEVAQUIN®. Other reasons that can increase your risk of tendon problems can include:**
    - physical activity or exercise
    - kidney failure
    - tendon problems in the past, such as in people with rheumatoid arthritis (RA).
- **Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation**. Stop taking LEVAQUIN® until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons.
- **Talk to your healthcare provider about the risk of tendon rupture with continued use of LEVAQUIN®**. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.
- **Tendon rupture can happen while you are taking or after you have finished taking LEVAQUIN®**. Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.
- **Get medical help right away if you get any of the following signs or symptoms of a tendon rupture**:
    - hear or feel a snap or pop in a tendon area
    - bruising right after an injury in a tendon area
    - unable to move the affected area or bear weight

2. **Worsening of myasthenia gravis (a disease that causes muscle weakness).** Fluoroquinolones like LEVAQUIN® may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section **"What are the possible side effects of LEVAQUIN®?"** for more information about side effects.

What is LEVAQUIN®?

LEVAQUIN® is a fluoroquinolone antibiotic medicine used in adults, 18 years or older, to treat certain infections caused by certain germs called bacteria.

Children have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems such as pain or swelling while taking LEVAQUIN®.

In children 6 months and older who have breathed the anthrax bacteria germ:

• LEVAQUIN® is used to prevent anthrax disease (inhalation anthrax).

• It is not known if it is safe to use LEVAQUIN® in children for more than 14 days.

It is not known if LEVAQUIN® is safe and works in children under the age of 6 months.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including LEVAQUIN®, do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking LEVAQUIN®.

Who should not take LEVAQUIN®?

Do not take LEVAQUIN® if you have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or if you are allergic to any of the ingredients in LEVAQUIN®. Ask your healthcare provider if you are not sure. See the list of the ingredients in LEVAQUIN® at the end of this Medication Guide.

What should I tell my healthcare provider before taking LEVAQUIN®?

See **"What is the most important information I should know about LEVAQUIN®?"**

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems

- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation."
- have low blood potassium (hypokalemia)
- have a history of seizures
- have bone and joint problems
- have kidney problems. You may need a lower dose of LEVAQUIN® if your kidneys do not work well.
- have liver problems
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if LEVAQUIN® will harm your unborn child.
- are breast-feeding or planning to breast-feed. LEVAQUIN® is thought to pass into breast milk. You and your healthcare provider should decide whether you will take LEVAQUIN® or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, herbal and dietary supplements. LEVAQUIN® and other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take LEVAQUIN® or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See **"What are the possible side effects of LEVAQUIN®?"**
- an oral anti-diabetes medicine or insulin
- a blood thinner (warfarin, Coumadin, Jantoven)
- a medicine to control your heart rate or rhythm (antiarrhythmics). See **"What are the possible side effects of LEVAQUIN®?".**
- an anti-psychotic medicine
- a tricyclic antidepressant
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See **"What is the most important information I should know about LEVAQUIN®?".**
- theophylline (Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®)
- Certain medicines may keep LEVAQUIN® from working correctly. Take LEVAQUIN® Tablets or Oral Solution either 2 hours before or 2 hours after taking these products:

- an antacid, multivitamin, or other product that has magnesium, aluminum, iron, or zinc.
- sucralfate (Carafate®)
- didanosine (Videx®,Videx® EC)

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take LEVAQUIN®?

- Take LEVAQUIN® exactly as prescribed by your healthcare provider.
- Take LEVAQUIN® at about the same time each day.
- Drink plenty of fluids while taking LEVAQUIN®.
- LEVAQUIN® Tablets can be taken with or without food.
- Take LEVAQUIN® Oral Solution 1 hour before or 2 hours after eating.
- If you miss a dose of LEVAQUIN®, take it as soon as you remember. Do not take more than one dose in one day.
- LEVAQUIN® for Injection is given to you by intravenous (I.V.) infusion into your vein, slowly, over 60 or 90 minutes, as prescribed by your healthcare provider. See "What are the possible side effects of LEVAQUIN®?"
- Do not skip any doses, or stop taking LEVAQUIN® even if you begin to feel better, until you finish your prescribed treatment, unless:
  - you have tendon effects (see "What is the most important information I should know about LEVAQUIN®?"),
  - you have a serious allergic reaction (see "What are the possible side effects of LEVAQUIN®?"), or
  - your healthcare provider tells you to stop.
- This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to LEVAQUIN®. If this happens, LEVAQUIN® and other antibiotic medicines may not work in the future.

If you take too much, call your healthcare provider or get medical help immediately.

If you have been prescribed LEVAQUIN® after being exposed to anthrax:

- LEVAQUIN® has been approved to lessen the chance of getting anthrax disease or worsening of the disease after you are exposed to the anthrax bacteria germ.

- Take LEVAQUIN® exactly as prescribed by your healthcare provider. Do not stop taking LEVAQUIN® without talking with your healthcare provider. If you stop taking LEVAQUIN® too soon, it may not keep you from getting the anthrax disease.
- Side effects may happen while you are taking LEVAQUIN®. When taking LEVAQUIN® to prevent anthrax infection, you and your healthcare provider should talk about whether the risks of stopping your medicine too soon are more important than the risks of side effects with LEVAQUIN®. It is not known if it is safe to use LEVAQUIN® for more than 28 days in adults and for more than 14 days in children 6 months of age and older.
- If you are pregnant, or plan to become pregnant while taking LEVAQUIN®, you and your healthcare provider should decide whether the benefits of taking LEVAQUIN® for anthrax are more important than the risks.

What should I avoid while taking LEVAQUIN®?

- LEVAQUIN® can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how LEVAQUIN® affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. LEVAQUIN® can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking LEVAQUIN®, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of LEVAQUIN®?

LEVAQUIN®can cause side effects that may be serious or even cause death. See "**What is the most important information I should know about LEVAQUIN®?"**

Other serious side effects of LEVAQUIN® include:

- **Liver damage (hepatotoxicity):** Liver damage (hepatotoxicity) can happen in people who take LEVAQUIN®. Call your healthcare provider right away if you have unexplained symptoms such as:
  - nausea or vomiting,
  - stomach pain,
  - fever,
  - weakness,
  - abdominal pain or tenderness,
  - itching,
  - unusual tiredness,

- loss of appetite,
- light colored bowel movements,
- dark colored urine or yellowing of your skin or the whites of your eyes.

- **Central Nervous System Effects**. Seizures have been reported in people who take fluoroquinolone antibiotics including LEVAQUIN®. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking LEVAQUIN® will change your risk of having a seizure.

Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of LEVAQUIN®. Talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:

- seizures
- hear voices, see things, or sense things that are not there (hallucinations)
- feel restless
- tremors
- feel anxious or nervous
- confusion
- depression
- trouble sleeping
- nightmares
- feel lightheaded
- feel more suspicious (paranoia)
- suicidal thoughts or acts
- persistent headache with or without blurred vision.

- **Serious allergic reactions**.

Allergic reactions can happen in people taking fluoroquinolones, including LEVAQUIN®, even after only one dose. Stop taking LEVAQUIN® and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:

- hives
- trouble breathing or swallowing
- swelling of the lips, tongue, face
- throat tightness, hoarseness
- rapid heartbeat

- faint
- Yellowing of the skin or eyes. Stop taking LEVAQUIN® and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to LEVAQUIN® (a liver problem).

- **Skin rash**

Skin rash may happen in people taking LEVAQUIN®, even after only one dose. Stop taking LEVAQUIN® at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to LEVAQUIN®.

- **Intestine infection (Pseudomembranous colitis)**

Pseudomembranous colitis can happen with most antibiotics, including LEVAQUIN®. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.

- **Changes in sensation and possible nerve damage (Peripheral Neuropathy)**

Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including LEVAQUIN®. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

- pain
- burning
- tingling
- numbness
- weakness

LEVAQUIN® may need to be stopped to prevent permanent nerve damage.

- **Serious heart rhythm changes** (QT prolongation and torsades de pointes) Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. LEVAQUIN® may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this happening are higher in people:
  - who are elderly
  - with a family history of prolonged QT interval
  - with low blood potassium (hypokalemia)
  - who take certain medicines to control heart rhythm (antiarrhythmics)

- **Changes in blood sugar [low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia)]**

People who take LEVAQUIN® and other fluoroquinolone medicines with oral anti-diabetes medicines or with insulin can get low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia). Follow your healthcare provider's instructions for how often to check your blood sugar. If you have diabetes and you get low blood sugar while taking LEVAQUIN®, stop taking LEVAQUIN® and call your healthcare provider right away. Your antibiotic medicine may need to be changed.

- **Sensitivity to sunlight (photosensitivity)**

See **"What should I avoid while taking LEVAQUIN®?"**

- **Joint Problems**

Increased chance of problems with joints and tissues around joints in children. Tell your child's healthcare provider if your child has any joint problems during or after treatment with LEVAQUIN®.

The most common side effects of LEVAQUIN® include:

- dizziness
- headache
- constipation
- nausea
- diarrhea

In children 6 months and older who take LEVAQUIN® to prevent anthrax disease, vomiting is also common.

Low blood pressure can happen with LEVAQUIN® given by IV injection if it is given too fast. Tell your healthcare provider if you feel dizzy, or faint during a treatment with LEVAQUIN®.

LEVAQUIN® may cause false-positive urine screening results for opiates when testing is done with some commercially available kits. A positive result should be confirmed using a more specific test.

These are not all the possible side effects of LEVAQUIN®. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LEVAQUIN®?

Store LEVAQUIN® Film-Coated Tablets at 59° to 86° F (15°C to 30°C). Keep the container closed tightly.

Store LEVAQUIN® Oral Solution at 59° to 86° F (15°C to 30°C).

Keep LEVAQUIN® and all medicines out of the reach of children.

General Information about LEVAQUIN®

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LEVAQUIN® for a condition for which it is not prescribed. Do not give LEVAQUIN® to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about LEVAQUIN®. If you would like more information about LEVAQUIN®, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about LEVAQUIN® that is written for healthcare professionals. For more information go to www.levaquin.com or call 1-800-526-7736.

What are the ingredients in LEVAQUIN®?

- 250 mg LEVAQUIN® Film-Coated Tablets:
  - Active ingredient: levofloxacin.
  - Inactive ingredients: hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.
- 500 mg LEVAQUIN® Film-Coated Tablets:
  - Active ingredient: levofloxacin.
  - Inactive ingredients: hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red and yellow iron oxides.
- 750 mg LEVAQUIN® Film-Coated Tablets:
  - Active ingredient: levofloxacin.
  - Inactive ingredients: hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80.
- LEVAQUIN® Oral Solution (25 mg/mL):
  - Active ingredient: levofloxacin.

- Inactive ingredients: sucrose, glycerin, sucralose, hydrochloric acid, purified water, propylene glycol, artificial and natural flavors, benzyl alcohol, ascorbic acid, and caramel color. It may also contain a solution of sodium hydroxide for pH adjustment.
    - LEVAQUIN® Oral Solution may look clear yellow to clear greenish-yellow in color.

- LEVAQUIN® Injection in Single-Use Vials:
    - Active ingredient: levofloxacin.
    - Inactive ingredients: water for injection. LEVAQUIN® for Injection Single Use Vials do not contain any preservatives.
- LEVAQUIN® Injection Premix in Single-Use Flexible Containers:
    - Active ingredient: levofloxacin.
    - Inactive ingredients: Dextrose (D_5W). Solutions of hydrochloric acid and sodium hydroxide may have been added to adjust the pH.

Revised October 2011

Active Ingredient Made in Japan

Finished Product Manufactured by:

- Janssen Ortho LLC, Gurabo, Puerto Rico 00778 (Tablets).
- Janssen Pharmaceutica N.V., Beerse, Belgium (Oral Solution, Injection Single-Use Vials).
- Hospira, Inc., Austin, TX 78728 (Injection Premix).

Manufactured for:

- Janssen Pharmaceuticals, Inc., Titusville, NJ 08560.

This Medication Guide has been approved by the U.S. Food and Drug Administration.